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ORIGINAL ARTICLE

Prognostic Factors for Post-recurrence Survival in Esophageal Squamous Cell Carcinoma Patients with Recurrence after Resection

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Abstract
Objective The survival of recurrent esophageal cancer is poor. But reports regarding prognostic factors for post-recurrence survival are limited. We analyzed the recurrence pattern and the prognostic factors for post-recurrence survival in esophageal squamous cell carcinoma with recurrence after resection.
Methods Two hundred sixty-eight patients were included. Tumor recurrence occurred in 115 (42.9%) patients. Recurrence pattern was classified as locoregional, distant, and combined recurrence. The post-recurrence survival was defined as the interval between initial recurrence and either death or the last follow-up.
Results Mediastinum lymphadenopathy was the most common site for locoregional recurrence, whereas lung, liver, and bone were the most common sites for distant recurrence. The overall 1- and 2-year post-recurrence survival rates were 32.6% and 12.6% with a median survival after recurrence of 6.0 months. The independent prognostic factors included liver recurrence (HR=2.255, 95%CI=1.073–4.741, p=0.032), time to recurrence ≤10 months (HR=2.657, 95%CI=1.438–4.911, p=0.002), and no treatment for recurrences (HR=2.745, 95%CI=1.635–4.608, p<0.001).
Conclusions We identify liver recurrence, early recurrence, and no treatment for recurrence as risk factors for dismal post-recurrence survival.

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Keywords Esophageal cancer · Recurrence · Squamous cell carcinoma · Surgery

Introduction

Esophageal cancer is one of the deadliest cancers with rapidly rising incidence.[1] Even after resection with curative intent, the 5-year survival is rarely >25%.[2] Furthermore, a large number of patients would suffer from tumor recurrences and more than 50% of tumor recurrences occur within 1 year after operation.[3–9] As for the patients with recurrent esophageal cancer after resection, only limited reports addressed the outcome after recurrence, and most indicated extremely poor prognosis. The median survival after recurrence is usually <1 year.[5–10] Many factors, such as tumor location, invasion depth, lymph node metastasis, degree of cell differentiation, vascular invasion, and lymphatic invasion, have been reported to affect survival

and recurrence in esophageal cancer patients.[4–6,8–11] In contrast, very little information regarding the predictors for post-recurrence survival in recurrent esophageal cancer after resection could be found in the literature. In this report, we retrospectively reviewed 268 patients who underwent esophagectomy for esophageal squamous cell carcinoma (ESCC). We aim to analyze the pattern of recurrences and investigate the prognostic factors for post-recurrence survival in patients with recurrence after esophagectomy and lymphadenectomy for ESCC.

Patients and Methods

Study population

A consecutive series of 381 patients who underwent esophagectomy for cancer at Taipei-Veterans General Hospital between 2000 and 2008 was studied. Preoperative staging included physical examination, laboratory tests, esophagogastroduodenoscopy, flexible bronchoscopy (for upper third and middle third tumors), barium esophagography, computed tomography (CT) scans from neck to upper abdomen, ultrasound of the abdomen, and radionuclide bone scans. The positron emission tomography/CT scan became a routine preoperative staging examination for esophageal cancer since 2007. The presence of lymph node enlargement was not a contradiction as long as the nodes are included in the resection. The exclusion criteria included: (1) patients with non-squamous cell carcinoma (n=37); (2) patients who received neoadjuvant chemoradiation (n=33), since the "T" and "N" status may be affected; (3) patients who did not received transthoracic esophagectomy (n=26) and thus the extent of intrathoracic lymphadenectomy may not be adequate; (4) patients with incidental findings of M1 stage during operation (n=9, lung (three), liver (two), omentum (three), and pleural seeding (one)); (5) patients with microscopic or macroscopic residual tumor cells at cut end (n=20); and (6) patients with in-hospital mortality (n=22, 5.8%). The Institutional Review Board of Taipei-Veterans General Hospital approved this study design.

Treatments

The surgical methods included transthoracic esophagectomy and left-sided thoracoabdominal approach. In the transthoracic esophagectomy, esophagectomy and systematic mediastinum lymph node dissection were performed in the thoracic stage. Esophageal substitute mobilization and dissection of paracardial nodes and enlarged celiac axis nodes were performed in the abdominal stage. Then, the gastric tube was pulled to the cervical incision for anastomosis. Cervical lymph node sampling was also completed in the cervical stage. In the left-sided thoracoabdominal approach, the incision extends from below the scapula, across the costal margin, and obliquely toward the umbilicus. The left side pleural cavity and abdominal cavity were exposed simultaneously. The principle of dissection in left-sided thoracoabdominal approach was similar to that of the transthoracic esophagectomy method. Determination of the pathological stage was according to the 7th edition AJCC TNM staging system.[12] Adjuvant therapy was offered to all patients with pT3/T4 stage and positive lymph node metastases.

Follow-up

All patients were followed-up at our outpatient department with an interval of 3 months for the first 2 years, 6 months for 2–5 years, and then annually. Routine follow-up exams include serum tumor marker, chest radiography, and CT scan from the neck to the upper abdomen. Endoscopy and radionuclide bone scans were obtained as clinically indicated. Diagnosis of recurrence was based on histological, cytological, or radiological evidences. Tumor recurrences were classified as locoregional recurrence, distant recurrence, and combined recurrence. Recurrences at the anastomotic site or within the area of previous resection and nodal clearance in the mediastinum or upper abdomen were classified as locoregional recurrence. Distant recurrence was defined as hematogenous metastasis to solid organs or recurrence in the pleura or peritoneal cavity. Simultaneous locoregional and distant recurrences were classified as combined recurrence. The interval between first treatment and detection of recurrence was defined as time to recurrence. The post-recurrence survival was defined as the interval between the detection of initial recurrence and either death or the last follow-up. The principle of treatment for recurrence followed the National Comprehensive Cancer Network (NCCN) guideline.[13] Recurrences were managed with best supportive care or palliative therapy depending on the patient's performance and the surgeon's decision. The palliative treatments included surgery, chemotherapy, radiotherapy, and combined chemoradiation. The best supportive care purposed to relieve patient's symptoms and supported the quality of life regardless of the stage of the disease and the need for further treatment.

Statistics

A chi-square test was used to compare categorical variables and ANOVA for the comparison of continuous variables.

Calculation of post-recurrence survival and construction of survival curve were performed by the Kaplan–Meier method. To assess the prognostic factors for post-recurrence survival, univariate and multivariate analyses by means of Cox regression model were used. To avoid overfitting and selection bias, the full model approach incorporating all candidate variables was used in the multivariate analysis.[14] All calculations were performed using SPSS 17.0 software, and a p value of <0.05 was considered significant.

Results

Patient Demographics and Recurrence Pattern

Two hundred sixty-eight patients met the criteria. The patient characteristics are summarized in Table 1. Patients with more advanced stage of disease tended to have a higher rate of recurrence. Adjuvant therapy was offered to all patients with T3/T4 stage or positive lymph node

Table 1 Characteristics of patients with and without recurrence

Variables	Recurrence					Total (n=268)
	Without (n=153)	Local (n=41)	Distant (n=50)	Combined (n=24)	p value	
Age, mean (±SD)	61.0 (12.1)	61.9 (11.2)	60.3 (10.7)	62.2 (12.1)	0.888	61.1 (11.7)
Sex					0.320	
Male	135	40	46	22		243
Female	18	1	4	2		25
Surgical approach					0.343	
Thoracotomy, three-hole	145	39	45	24		253
Left thoracoabdominal	8	2	5	0		15
T					0.024*	
1	37	9	4	1		51
2	35	9	11	2		57
3	69	22	32	17		140
4	12	1	3	4		20
N					0.002*	
0	75	21	11	10		117
1	46	12	14	8		80
2	15	7	17	5		44
3	17	1	8	1		27
Stage					0.001*	
I	26	9	1	1		37
II	69	16	13	9		107
III	58	16	36	14		124
Grade					0.172	
Well-differentiated (G1)	22	3	6	4		35
Moderately differentiated (G2)	121	34	36	15		206
Poorly differentiated (G3)	10	4	8	5		27
Location					0.551	
Upper third	16	4	4	3		27
Middle third	102	26	27	16		171
Lower third	35	11	19	5		70
Tumor length (cm)	4.4 (2.3)	4.3 (1.9)	5.1 (2.0)	5.9 (2.6)	0.006*	4.7 (2.3)
Chemoradiation status					0.008*	
None	104	30	22	17		173
Adjuvant chemoradiation	49	11	28	7		95

A chi-square test was used to compare categorical variables and ANOVA for comparison of continuous variables

SD standard deviation

*p<0.05

Table 2 Pattern of recurrence in 115 patients

	No. of patients (%)
Locoregional recurrence	41 (35.7)
Distant recurrence	50 (43.5)
Combined recurrence	24 (20.9)
Locoregional recurrence	65
Mediastinum lymphadenopathy	39 (60.0)
Cervical lymphadenopathy	13 (20.0)
Anastomosis	9 (13.8)
Celiac lymphadenopathy	7 (10.8)
Distant metastasis	74
Lung	35 (47.3)
Liver	23 (31.1)
Bone	18 (24.3)
Pleural effusion	10 (13.5)
Brain	5 (6.8)
Other abdominal organ	6 (8.1)

metastases; however, only 95 patients completed the whole course of therapy.

During a mean follow-up of 27 months, tumor recurrence after resection developed in 115 patients (115/268, 42.9%). The median time to recurrence was 10 months. More than half (75/115, 66.2%) recurrences happened within 1 year after operation. The patterns of recurrences included locoregional only in 41 (41/115, 35.7%) patients, distant only in 50 (43.5%) patients, and combined recurrences in 24 (20.9%) patients (Table 2). For locoregional recurrences, 39 (39/65, 60.0%) patients presented with mediastinum lymphadenopathy, 13 (20.0%) had cervical lymphadenopathy, 7 (10.8%) had celiac lymphadenopathy, and 9 (13.8%) patients had locoregional recurrence at the anastomostic site. For distant recurrences, 35 (35/74, 47.3%) patients presented with lung, 23 (31.1%) with liver, 18 (24.3%) with bone, 10 (13.5%) with malignant pleural effusion, 5 (6.8%) with brain, and 6 (8.1%) with other intra-abdominal organs metastases. Treatments for recurrences included surgery for 1 patients, chemotherapy for 33 patients, radiotherapy for 12 patients, and combined chemoradiation for 28 patients. Forty patients received best supportive care due to poor performance status.

Factors Predicting Post-recurrence Survival

The overall 1- and 2-year post-recurrence survival rates were 32.6% and 12.6% (Fig. 1). Median survival after recurrence was 6.0 months (95% CI=5.6–8.4 months). Univariate analysis (Table 3) identified tumor invasion depth, tumor length, combined type recurrence, liver metastasis, time to recurrence, and treatment for recurrences as prognostic factors for post-recurrence survival. In the multivariate analysis (Table 4), liver metastasis, time to recurrence, and treatment for recurrences remained independent prognostic factors for post-recurrence survival.

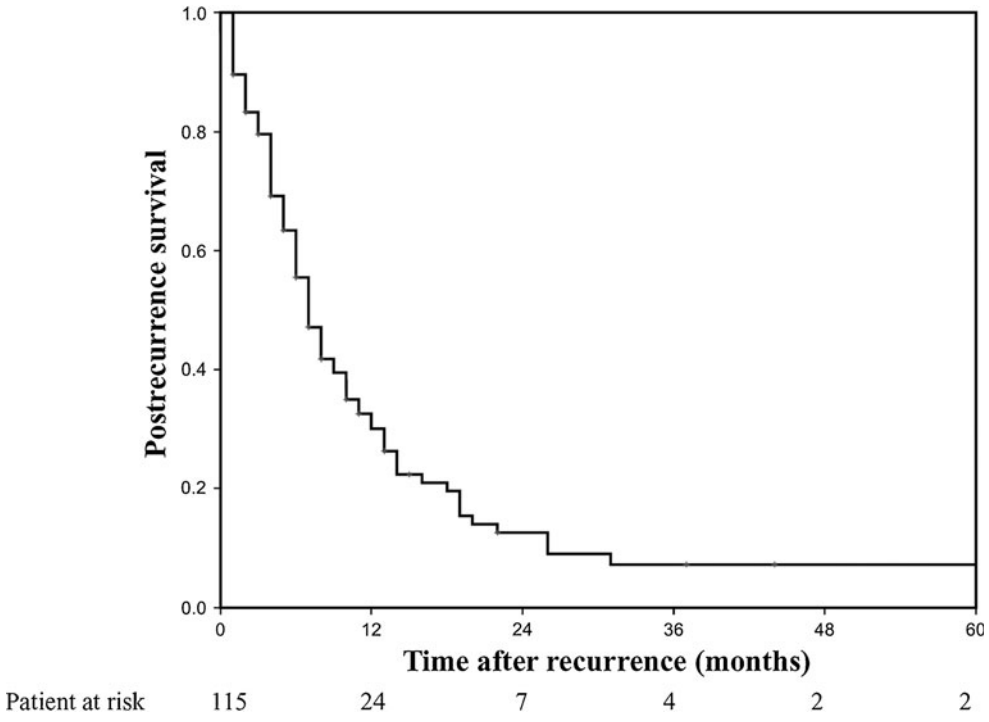


Fig. 1 Post-recurrence survival in 115 patients with recurrent esophageal cancer after esophagectomy. Survival curves were plotted by the Kaplan–Meier method

Table 3 Univariate analysis for post-recurrence survival in 115 patients with recurrent esophageal cancer after esophagectomy

Variables	HR	95% CI	*p* value
Age	1.001	0.981–1.021	0.931
Sex			
Male	1	–	–
Female	1.101	0.402–3.015	0.852
Surgical approach			
Thoracotomy, three-hole	1	–	–
Left thoracoabdominal	0.994	0.735–1.346	0.971
T			
1	1	–	–
2	1.203	0.529–2.736	0.659
3	1.842	0.900–3.770	0.095
4	3.552	1.295–9.743	0.014*
N			
0	1	–	–
1	1.611	0.959–2.704	0.071
2	1.277	0.719–2.270	0.404
3	1.606	0.752–3.430	0.221
Stage			
I	1	–	–
II	1.141	0.499–2.606	0.755
III	1.589	0.718–3.516	0.253
Grade			
Well differentiated (G1)	1	–	–
Moderately differentiated (G2)	0.610	0.320–1.163	0.133
Poorly differentiated (G3)	0.469	0.201–1.091	0.079
Location			
Upper third	1	–	–
Middle third	1.084	0.531–2.213	0.826
Lower third	1.195	0.511–2.343	0.816
Tumor length (cm)	1.124	1.024–1.234	0.014*
Chemoradiation status			
None	1	–	–
Adjuvant chemoradiation	1.106	0.889–1.378	0.366
Recurrence type			
Local only	1	–	–
Distant only	1.548	0.953–2.516	0.078
Combined	2.264	1.269–4.037	0.006*
Local recurrence site			
Mediastinum (with vs without)	0.895	0.570–1.405	0.630
Cervical (with vs without)	0.696	0.369–1.314	0.264
Celiac (with vs without)	1.568	0.693–3.281	0.300
Anastomosis (with vs. without)	1.220	0.562–2.650	0.615
Distant metastasis site			
Lung (with vs. without)	1.245	0.780–1.986	0.359
Liver (with vs. without)	2.506	1.447–4.339	0.001*
Bone (with vs. without)	1.592	0.891–2.845	0.116
Brain (with vs. without)	1.061	0.386–2.920	0.909
Pleural effusion (with vs. without)	1.583	0.758–3.306	0.222
Abdominal organ (with vs. without)	1.315	0.530–3.260	0.555
Time to recurrence			
>10	1	–	–
≤10	2.231	1.440–3.456	<0.001*
Treatment for recurrence			
Yes	1	–	–
No	1.952	1.272−2.997	0.002*

Analysis was performed using the Cox regression model

HR hazard ratio, *CI* confidence interval

*$p<0.05$

Liver is the only distant metastasis site that predicted worse survival. When stratified by median time to recurrence (10 months), patients with early recurrence (≤10 months) had worse survival. In contrast, palliative treatments, instead of supportive care only, for recurrence was a favorable factor for post-recurrence survival. Patients with more risk factors (liver recurrence, early recurrence, and no treatment for recurrence) would suffer from poorer post-recurrence survival (Fig. 2). The median survival in patients with zero, one, two, and three risk factors were 14 (95% CI=8.7–19.3), 7 (95% CI=5.2–8.8), 4 (95% CI=1.6–6.4), and 2 (95% CI=1.1–2.9), respectively ($p<0.001$). One year post-recurrence survival rate was 61.75%, 30.7%, and 4.3% for patients with zero, one, and two risk factors, respectively, whereas none with three risk factors survived more than 1 year.

Discussion

Pattern of tumor recurrence differs among types of cancers. In some types of cancers, recurrence may arise soon after

Table 4 Significant variables in multivariate analysis for post-recurrence survival in 115 patients with recurrent esophageal cancer after esophagectomy

Variables	HR	95% CI	*p* value
Liver (with vs. without)	2.255	1.073–4.741	0.032
Time to recurrence (≤10 vs. >10 months)	2.657	1.438–4.911	0.002
Treatment for recurrence (no vs. yes)	2.745	1.635–4.608	<0.001

Analysis was performed using the Cox regression model. The full model approach incorporating all candidate variables was used. Only significant variables were listed

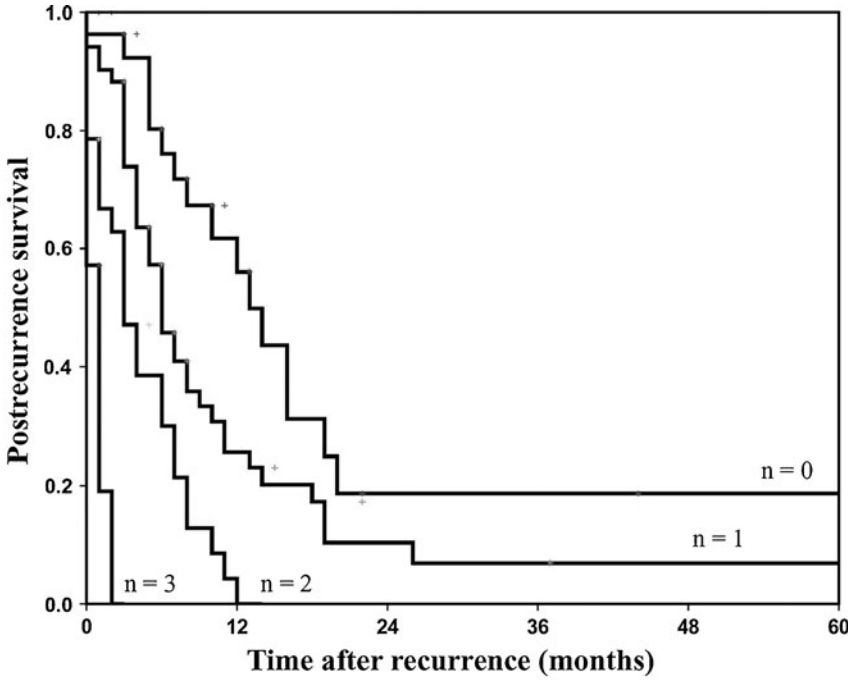
HR hazard ratio, C*I* confidence interval

*$p<0.05$

primary treatment, whereas in others it occurs years after. The disseminated cancer cells may even survive in distant organ microenvironment in a dormant state until they meet all requirements for metastatic outgrowth.[15] The concept of "tumor self-seeding" by circulating cancer cells also explains the early development of locoregioanl recurrence after tumor resection in some cancers.[16] An awareness of recurrent pattern in each type of cancer is essential to patient follow-up protocol.[6] Understanding the predictive factors for post-recurrence survival helps identify high-risk patients, select appropriate treatments, and improve patient outcome after recurrence.

The reported recurrence rate after curative resection for esophageal cancer ranges from 36.8% to 59.2%.[7,17] Locoregional recurrences may occur along the entire "esophageal bed" from the cervical lymph node, anastomostic site, and the mediastinum to intra-abdominal lymph nodes with different frequencies according to the primary localization of tumor.[3,17,18] As for the distant recurrence, the most common involved organs were the lung, liver, and bone in most reports.[3–5,8,17,19] In some reports, soft tissue and skin were also frequent sites for distant recurrence.[3,5,17] In a study by Smit et al.,[17] 40.3% of distant recurrences were noted in the skin or soft tissue, which was the most frequent site for distant recurrences. In our study, the most common sites for distant recurrences were the lung, liver, and bone, followed by the malignant pleural effusion, brain, and other intra-abdominal organs including the spleen, kidney, pancreas, and adrenal glands.

The prognosis of recurrent esophageal cancer is extremely poor. The median post-recurrence survival ranges between 2.7 and 10.0 months in the literature.[5–10] Dresner and Griffin[5] reported the recurrence pattern following radical esophagectomy with two-field lymph node dissection in 176 patients. Among 85 patients with proven recurrences, the median post-recurrence survival was only 2.7 months. They also showed a relative survival advantage in patients with cervical recurrence, but there was no survival difference in patients with interventional therapy compared with those with symptomatic treatment alone. In contrast with Dresner and Griffin's observation, Kunisaki et al.[10] studied 166 patients who underwent curative esophagectomy. Seventy-two developed recurrence, and they identified that each treatment, including chemotherapy, radiotherapy, and chemoradiation, significantly affected survival after recurrence. Abate et al.[6] also showed that



Patient at risk

Risk factor number (n)						
0	29	11	2	2	1	1
1	51	12	5	2	1	1
2	28	1				
3	7					

Fig. 2 Three prognostic factors including liver recurrence, early recurrence, and no treatment for recurrence were identified as risk factors for poor post-recurrence survival. The median survival in patients with zero, one, two, and three risk factors were 14 (95% CI=8.7–19.3), 7 (95% CI=5.2–8.8), 4 (95% CI=1.6–6.4), and 2 (95% CI=1.1–2.9), respectively ($p<0.001$). Patients with more risk factors would suffer from poorer post-recurrence survival. Survival curves were plotted by the Kaplan–Meier method

median post-recurrence survival was significantly longer in patients treated for recurrence (9 vs. 3 months, $p=0.001$).

With regard to the type of recurrence, Mariette et al.[8] reported a significantly longer median post-recurrence survival for regional dissemination than for distant recurrence. They also demonstrated that patients with cervical recurrence had significantly longer survival than those with recurrence at other sites, which was similar to the observation in reports by Dresner and Griffin and Kato et al.[5,20] However, Bhansali et al.[9] reported no difference in different types of recurrences. The median post-recurrence survival was 7 and 9 months in patients with locoregional and distant recurrence, respectively, after radical esophagectomy for ESCC in their study.

Another reported prognostic factor for post-recurrence survival is the interval from esophagectomy to detection of recurrence. Osugi et al.[21] indicted that the time to recurrence correlated with survival after recurrence in ESCC patients who underwent esophagectomy and extended lymphadenectomy. Shimada et al.[7] also showed that patients with time of recurrence <1 year had worse 1-year survival after treatment for recurrence. In accordance with previous literature, we also showed treatment for recurrence and time to recurrence as prognostic factors for post-recurrence survival. Whereas chemotherapy or radiation for recurrence was a favorable factor for post-recurrence survival, patients with early recurrence (time to recurrence ≤10 months) suffered worse prognosis. In addition, we identified liver metastasis as an independent prognostic factor for post-recurrence survival. Liver recurrence was noted in 23 of 115 patients with recurrent esophageal cancer in the current study. The 1-year post-recurrence survival rate in patients with recurrence other than liver was 36.3%, whereas none with live recurrence survived more than 1 year. The post-recurrence survival was significantly shorter in the presence of liver metastasis. In contrast, distant recurrence at other organs had no prognostic value on survival after recurrence.

The current study presented the results of a "surgical series." Since multidisciplinary approaches which highlight the importance of neoadjuvant chemoradiation have shown the survival benefits, we have changed our policy and followed the NCCN guideline using induction chemoradiation.[13,22] Further comparison on the post-recurrence survival difference between patients with and without neoadjuvant chemoradiation is needed. In summary, 115 of 268 ESCC patients developed recurrences after esophagectomy and lymphadenectomy. The survival after recurrence is very poor, with 1- and 2-year post-recurrence survival of 32.6% and 12.6%. We identify T3/T4 stage, liver recurrence, early recurrence, and no treatment for recurrence as risk factors for poor post-recurrence survival. Patients with more risk factors would suffer from poorer post-recurrence survival. Our results may provide a guide to identify high-risk patients, select appropriate treatments, and improve patient outcome after recurrence.

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