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Association of lymphadenectomy and survival in epithelial ovarian cancer

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ABSTRACT

Purpose: Lymph node metastasis has a significant contribution to the prognosis of epithelial ovarian cancer but the role of lymph node dissection in treatment is not clear. In this study, we aimed to retrospectively determine the effect of the number and localization of lymph nodes removed and the number of metastatic lymph nodes on survival.

Methods: In this study, we retrospectively reviewed the data of 378 patients (210 patients with lymph node dissection and 168 patients with no dissection) who underwent primary surgery between 2004 and 2014 in various centers with epithelial ovarian cancer diagnosis and followed up in our medical oncology clinic. Demographic and histopathologic features, stage, Ca 125 levels, chemotherapy responses of these patients were examined and survival analyzes were performed.

Results: The median age of the patients was 52 years (range 16-89) and median follow-up duration was 39 months (range 1-146). During the analysis, 156 patients (41%) died and 222 patients (59%) were alive. Patients who underwent lymphadenectomy had significantly improved progression free survival (PFS) (18 vs 31 months, $P < 0.05$) and overall survival (OS) (57 vs 92 months, $P < 0.05$). OS was longer in patients with >10 lymph nodes removed compared to patients with 1-10 lymph nodes removed ($P = 0.005$). Survival

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was found to be longer in patients with pelvic and paraaortic lymph node dissection compared to patients with only pelvic lymph node dissection ($P < 0.05$). Patients in stage I-II had no difference in PFS and OS. Patients in stage III-IV had no difference in PFS but there was a significant difference in OS ($P = 0.02$).

Conclusion: It may be a therapeutic effect of lymphadenectomy in advanced stage ovarian cancer. The number of lymph nodes removed and the removal of the paraaortic lymph nodes may also contribute to the treatment.

Background

Despite of improvements in treatment of epithelial ovarian cancer, it is still the most common gynecological cancer that results in death,[1] because most of the patients present with bulky intraperitoneal advanced-stage disease. More than two-thirds of patients with EOC are diagnosed at advanced stage due to lack of symptoms and effective screening methods.[2] Five-year survival is 80% at early stage, while it is approximately 30% at advanced stage.[3]

Major type of spread in EOC is intraperitoneal but retroperitoneal spread is also frequent at all stages. It is the cancer among genital cancers in which spread via lymph nodes is most commonly seen.[4] Lymph node metastasis is related with poor prognosis.[1,5–8] It is present in 10%-15% of the cancers that are localized in ovary and in 50% of advanced-stage cancers.[9]

The standard treatment is primary cytoreductive surgery with combined chemotherapy containing taxane and platin. Surgical treatment is individualized, as dissemination of each tumor and characteristics of the disease are different.[10] Although lymph node dissection is required for accurate staging and adequate treatment in early-stage ovarian cancer, its effect on survival is not clear.[11] Lymph node dissection comprises an important part of an optimal cytoreduction in advanced stage patients. However, there has been no consensus yet regarding whether systematic lymphadenectomy leads to improvement in survival.[1,12,13] In this study, we aimed to investigate the role of lymphadenectomy on survival in patients followed-up with EOC in our clinic.

Materials and methods

The data of 474 stage I-IV primary epithelial ovarian cancer patients treated and followed in our medical oncology clinic between 2004 and 2014 were retrospectively collected. Patients who had borderline ovarian malignancy or were receiving neoadjuvant chemotherapy or had not undergone primary surgery was excluded from the study. We analyzed the remaining 378 patients' data. All patients had primary surgery and were surgically staged according to the International Federation of Gynecology and Obstetrics system.

The following features were analyzed and reported: demographic features, preoperative serum Ca 125 levels, type of surgery, chemotherapy, residual disease after primary cytoreductive surgery, International Federation of Gynecology and Obstetrics stage, histological type, tumor grade, number of resected lymph nodes, lymphadenectomy region, optimal or suboptimal surgery, recurrence, progression free survival time, and overall survival times.

After primary surgery 299 patients (79%) received adjuvant chemotherapy—carboplatin (area under the curve; 5-6) and paclitaxel (175 mg/m^2) based systemic combination chemotherapy, every 3 weeks for 3-9 cycles. At the end of the surgical and/or adjuvant treatment, the treatment response was evaluated as partial response, complete response or progression. Residual

disease after primary surgery was described as optimal surgery (no gross residual disease or residual disease size 0.1-1 cm in the largest diameter) or suboptimal surgery (residual disease size >1 cm in the maximal diameter of the largest tumor nodule). Optimal surgery rate was 90% (340 out of 378 patients). One hundred eighty six (49%) patients were operated in the gynecologic oncology department of our hospital and 192 patients (51%) were operated at different centers. Therefore, there may be surgical differences between patients due to different surgeons and applied techniques. The decisions of lymphadenectomy, lymph node sampling, or dissection were given by the surgeon based on intraoperative tumor prevalence.

We retrospectively reviewed the operative pathology reports of patients in the medical oncology clinic. Patients were divided into 2 groups according to lymph node dissection performed or not. Two hundred ten patients had lymph node dissection and 168 patients did not have lymph node dissection. Patients with at least 1 lymph node removed were grouped according to number of lymph nodes removed as ≤10 and >10. Additionally, patients were grouped according to the stage of the disease as early stage (stage I-II) and advanced stage (stage III-IV). They were also evaluated in 2 groups according to the regions that lymphadenectomy was performed to pelvic region and pelvic + paraaortic region.

For descriptive statistics of data, mean, standard deviation, median lowest value, median highest value, frequency, and rates were used. Various clinical and pathologic factors were compared with Pearson's $\chi 2$ test for categorical data. Independent samples *t* test and Mann Whitney *U* test statistic for continuous data according to normality. Overall survival (OS) and progression-free survival (PFS) were calculated using the Kaplan-Meier method. Prognostic factors were compared using the log-rank test in univariate analysis. Univariate and multivariate analysis for assessing the influence of various prognostic factors on survival was performed using the Cox proportional hazards model. All *P* values were 2-sided in the tests and *P* values of less than 0.05 were considered to be statistically significant. For statistical analyses SPSS version 17.0 was used.

Results

The median age of the patients was 52 years (range 16-89), median PFS was 25 months and median OS was 75 months. Five-year OS rate was 55%, 78%, 35% for all stages, stage 1I-II, stage III-IV, respectively. Median follow-up duration was 39 months (range 2-146). In all patients, the median number of lymph nodes removed was 10 (range 0-100). In the group that at least 1 lymph node was removed, the median number of removed lymph nodes was 19 (range 1-100), the ratio of metastatic lymph node was 22% (Table 1). The patients in the group without lymphadenectomy were older. There was a difference in the stage, ECOG PS (Table 2).

Patients who underwent lymphadenectomy had significantly improved PFS (18 vs 31 months, $P < 0.05$) and OS (57 vs 92 months, 5-year survival rate of 88% and 72%, respectively, $P < 0.05$) (Fig 1) (Table 3). The median survival time was longer in patients with >10 lymph nodes removed compared to patients with no or 1-10 lymph nodes removed ($P < 0.05$). There was no significant difference in terms of survival between patients with no lymph node removed and 1-10 lymph nodes removed (Fig 2).

In univariate model, the age of the patient (≤65, >65), the stage of the disease (1-2, 3-4), the grade of the disease (I-II, III), the status of lymph node dissection (yes/no), the number of lymph nodes removed (1-10, >10), the region of removed lymph nodes (pelvic, pelvic plus paraaortic), ECOG-PS (0, ≥1) had significant effects on survival time ($P < 0.05$). Effect of the stage of the disease, the age of the patients and the number of lymph nodes removed on survival was demonstrated with multivariate analysis (Table 4).

We examined 2 separate groups as stage I-II and stage III-IV. Progression-free survival time did not differ significantly between groups with respect to dissection of lymph node ($P > 0.05$). PFS differed significantly with respect to the number of lymph nodes removed (>10 vs 1-10) (stage I-II; $P = 0.05$, stage III-IV; $P = 0.006$). Stage III-IV patients who underwent lymphadenectomy had significantly improved OS (37 vs 57 months, $P = 0.021$). Survival was found to be longer in stage III-IV patients with pelvic and paraaortic lymph node dissection compared to

Table 1
Follow-up and treatment characteristics.

		Min	-	Max	Median	n	%
Follow-up duration (Months)		2	-	146	38.7		
Status	Died					156	41.3
	Alive					222	58.7
Progression-free survival					25		
Relapse or progression	No					230	60.8
	Yes					148	39.2
Operation type	Nonlymphadenectomy					168	44.4
	Lymphadenectomy					210	55.6
Number of lymph nodes dissected		0	-	100	10		
Number of lymph nodes	0					168	44.4
	1-5					40	10.6
	6-10					38	10.1
	11-20					63	16.7
	>20					69	18.3
Lymphadenectomy region	Pelvic					126	60.0
	Pelvic + Paraaortic					84	40.0
Number of metastatic lymph nodes		0	-	33	1.28		
Metastatic lymph nodes	No					163	77.6
	Yes					47	22.4

patients with only pelvic lymph node dissection ($P = 0.013$), but that was not the case in stage I-II patients.

In evaluation that we did by dividing the patients into 5 groups according to number of lymph nodes removed as 0, 1-5, 6-10, 11-20, and >20, the increase in number of lymph nodes removed improved progression-free survival ($P = 0.001$). Moreover, in stage III-IV of the disease, improvement in survival was also shown and this effect was supported by multivariate analysis (HR = 0.74; 95% CI, 0.58-0.95; $P = 0.02$). There was no correlation between number of lymph nodes removed and number of metastatic lymph nodes (r = 0,068/$P = 0.326$). In stage IIIC patients having metastatic lymph nodes, when patients were divided into 2 groups as having 1-3 positive lymph nodes and ≥4 lymph nodes, there were no difference in progression-free survival and OS.

Discussion

EOC is the genital cancer in which lymphatic spread is seen most frequently. Lymphatic metastasis and lymphadenectomy are the most analyzed issues in EOC during the last 2 decades.[4,14]

There are 3 meta-analysis in the literature which indicate the survival effect of lymphadenectomy. In 2016, J Zhou et al conducted a meta-analysis of 556 patients (3 randomized controlled trials and 11 retrospective studies).[15] In this meta-analysis, lymphadenectomy was associated with more progression-free survival in randomized clinical trials, but not retrospective trials. Lymphadenectomy was associated with a 5-year overall survival in patients with both early and advanced stage cancer, but only with progression-free survival and a lower recurrence rate in patients with advanced stage cancer. In the 2 previous meta-analyses, lymphadenectomy was shown to increase 5-year OS in patients with advanced stage cancer, but not in early stage patients.[16,17]

In our study, 474 (stage I-IV) patients with EOC, PFS, and OS were significantly better in patients with lymphadenectomy compared to those without lymphadenectomy. Multivariate analysis was performed to analyze the impact of the number of lymph nodes removed (1-10 or >10) on survival. There were differences in the clinopathologic features of patients with and without lymphadenectomy. Patients without lymphadenectomy had higher median age and stage IV

Table 2
Clinicopathological data of all stage epithelial ovarian cancer patients (with or without lymphadenectomy).

		Non-lymphadenectomy n: 168 (%)	Lymphadenectomy n: 210 (%)	All patients n: 378 (%)	*P*
Age (median)		56	50	52.0	***0.000***
Stage					***0.036***
	1	68 (40.5)	75 (35.7)	143 (37.8)	
	2	9 (5.4)	25 (11.9)	34 (9)	
	3	78 (46.4)	103 (49)	181 (47.9)	
	4	13 (7.7)	7 (3.3)	20 (5.3)	
Grade					0.575
	1	31 (18.5)	30 (14.3)	61 (16.1)	
	2	59 (35.1)	69 (32.9)	128 (33.9)	
	3	62 (36.9)	90 (42.9)	152 (40.2)	
	Unknown	16 (9.5)	21 (10)	37 (9.8)	
ECOG-PS					***0.024***
	0	87 (51.8)	133 (63.3)	220 (58.2)	
	≥1	81 (48.2)	77 (36.7)	158 (41.8)	
Adjuvant therapy					*0.541*
	No	35 (20.8)	44 (21)	79 (20.9)	
	Carboplatin plus paclitaxel	133 (79.2)	166 (79)	299 (79.1)	
Adjuvant therapy response					
	Complete response	109 (82)	141(84.5)	250 (83.6)	0.373
	Partial response	9 (6.8)	12 (12)	21 (7)	
	Progression	15 (11.3)	13 (13)	28 (9.4)	
Histological type					0.976
	Serous	123 (73.2)	156 (74.3)	279 (73.8)	
	Mucinous	12 7.1()	15 (7.1)	27 (7.1)	
	Clear cell	8 (4.8)	12 (5.7)	20 (5.3)	
	Endometrioid	5 (3)	5 (2.4)	10 (2.6)	
	Other	20 (11.9)	22 (10.5)	42 (11.1)	
Residual disease after surgery					0.495
	No or <1cm	149 (88.7)	191 (91)	340 (89.9)	
	>1cm	19 (11.3)	19 (9)	38 (10.1)	
Ca 125 (units/ml)					0.896
	≤500	61 (57.5)	76 (56.3)	139 (57.2)	
	>500	45 (42.5)	59 (43.7)	104 (42.8)	

disease rate and ECOG PS ≥1 rate. Survival data may have been affected by these patient characteristics.

Systematic lymphadenectomy may cause upstaging in patients with clinically early stage disease limited to pelvis which, in turn, enables the patients to receive sufficient adjuvant chemotherapy. But there is no evidence showing that it is an independent prognostic factor. There are different results in the literature on the prognostic effect of lymphadenectomy in early stage ovarian cancer.[18-22] In a retrospective study of T1 ovarian cancers,[20] lymphadenectomy showed survival benefit, but in a randomized trial on T1 and T2 cancers its survival benefit was not demonstrated.[21] In a randomized clinical study, in which the effect of lymphadenectomy on survival in early-stage ovarian cancer was evaluated, systematic lymphadenectomy did not contribute to survival compared to lymph node sampling.[23] In our study, dissection of lymph node and its number in stage I-II patients had no effect on survival ($P > 0.05$). But progression-free survival was found to be longer in patients with >10 lymph nodes removed than 1-10 lymph nodes removed.

Cytoreductive surgery is one of the cornerstones in management of ovarian cancer. Lymphadenectomy comprises an important part of cytoreductive surgery, but its therapeutic value is still controversial. The contribution of number and region of lymph node dissection to survival

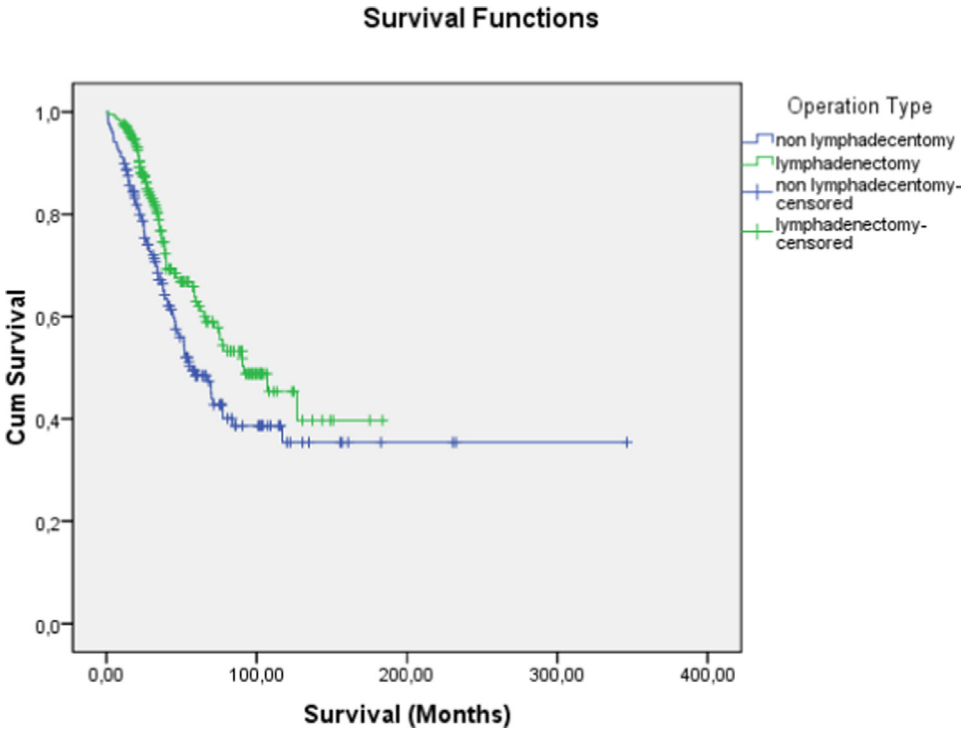

Fig. 1. Overall survival (OS) in patients with or without lymphadenectomy.

Table 3
Effect of clinical and surgical characteristics on overall and progression free survival.

			PFS				OS			
			mo	95% CI		*P*	mo	95% CI		*P*
		n		Lower	Upper			Lower	Upper	
Age, years	≤65	313	28	19.4	36.6	***0.002***	91	61.5	121.5	***0.000***
	>65	65	19	15.3	22.6		34	28.1	39.5	
ECOG PS	0	220	31	21	40.9	***0.002***	-	-	-	***0.000***
	≥1	158	19	14.2	23.8		51.5	36.1	66.8	
Stage	I-II	177	47	30.7	63.2	***0.000***	-	-	-	***0.000***
	III-IV	201	18	14.9	21.1		40.6	33.8	47.2	
Grade	I-II	189	32	19.7	42.2	***0.000***	-	-	-	***0.000***
	III	152	18	14.3	21.6		51.9	39.9	67.3	
Lymphadenectomy	No	168	18	13.2	22.8	***0.009***	57.3	43.8	70.8	***0.014***
	Yes	210	31	21.6	40.3		91.5	62.2	120.9	
Number of lymph nodes removed	1-10	78	21	13.8	28.2	***0.000***	65	32	99.4	***0.005***
	>10	132	56	23.8	88.2		-	-	-	
Lymphadenectomy region	Pelvic	126	27	19.1	34.9	***0.020***	75	46	104.1	***0.039***
	Pelvic + paraaortic	84	56	10.2	101.8		126	75.9	177.7	
Ca-125 (units/ml)	≤500	139	32	14.5	49.1	***0.007***	77	45	109.5	0.093
	>500	104	18	13.4	22.5		51	51.6	82.9	
Residual disease after surgery	No or <1cm	340	27	22.1	31.9	***0.029***	75	59.2	91.5	0.406
	> 1cm	38	18	13.2	22.7		46	19.9	72.1	

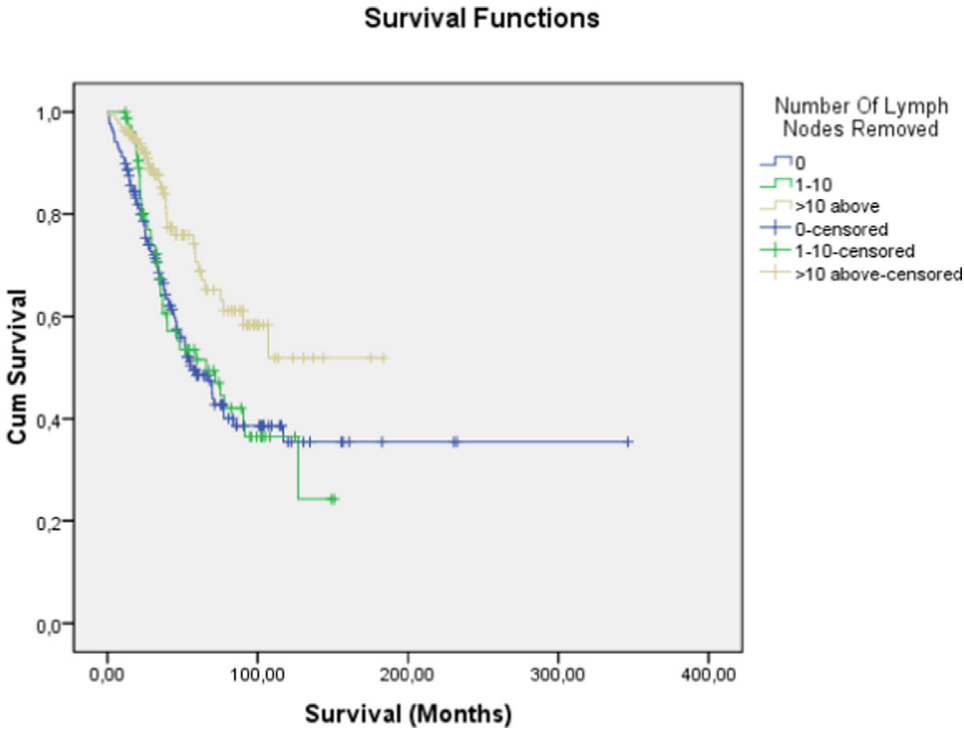

Fig. 2. Overall survival (OS) in patients w.r.t. number of lymph nodes removed.

in advanced-stage ovarian cancer has been demonstrated in many studies.[24-30] In a randomized clinical study conducted by Benedetti Pacini et al to evaluate the role of systematic lymphadenectomy in advanced-stage patients in 2005, it was shown that systematic lymphadenectomy improved 6-month disease-free survival compared to lymph node sampling.[14] In a retrospective study (stage IIIC, in 189 patients) both PFS and OS were better in patients with systemic lymphadenectomy.[27] In another study, conducted by Burghardt et al where 82 patients diagnosed with stage III EOC who were grouped as pelvic lymphadenectomy performed and not performed, 5-year survival rates were 54%, 13% respectively.[31] Similarly, in a SEER meta-analysis conducted in 2007, where 13 918 stage III-IV patients were divided into 6 groups according to number of lymph nodes removed (0, 1, 2-5, 6-10, and 11-20), it was shown that 5-year survival was improved as lymph node dissection increased.[1] Similar results have been obtained in our study. When the patients grouped based on the number of lymph nodes removed as, 1-5, 6-10, 11-20, and >20, progression-free survival and median survival time was found to be significantly better with increasing number of lymph nodes removed in stage III-IV patients ($P < 0.05$).

Retroperitoneal lymph node involvement occurs in nearly 4%-25% of women with early ovarian cancer, and 50%-80% of women with advanced ovarian cancer.[19] Previous studies mainly focused on systematic pelvic lymphadenectomy. It has also been suggested that nodal ovarian cancer metastases may be less sensitive to systemic chemotherapy because of diminished blood supply, and thus lymphadenectomy in patients with advanced disease is therapeutic as a result of maximal debulking.[32]

In a study conducted in 2014 concerning this issue, an improvement in survival was demonstrated with dissection of paraaortic lymph nodes in patients with positive metastatic lymph node.[33] In our study, survival was found to be improved in patients with pelvic and paraaortic lymph nodes removed than only pelvic lymph node removed.

Table 4
Cox-regression model of overall survival (OS) in ovarian cancer.

	Univariate analysis				Multivariate analysis			
	HR	95 % CI		*P*	HR	95 % CI		*P*
		Lower bound	Upper bound			Lower bound	Upper bound	
Age (≤65, >65)	2.58	1.81	3.67	***0.000***	2.4	1.33	4.35	***0.004***
Stage (1-2, 3-4)	4.33	3	6.26	***0.000***	4.53	2.49	8.24	***0.000***
Grade (1-2, 3)	1.93	1.37	2.71	***0.000***				
Operation Type (Non-lymphadenectomy, Lymphadenectomy)	0.67	0.49	0.92	***0.015***				
Number of lymph nodes dissected (1-10, >10)	0.5	0.32	0.82	***0.006***	0.56	0.34	0.93	***0.026***
Number of metastatic lymph nodes (<4, ≥4)	0.96	0.41	2.24	0.932				
ECOG-PS (0, ≥1)	2.38	1.73	3.29	***0.000***				
Lymphadenectomy Region (pelvic, pelvic + paraaortic) Cox-regression	0.58	0.34	0.97	***0.039***				

Our study has some features that might be viewed as potential weaknesses. First is the retrospective design of the study. Second is some of the patients were operated in different clinics other than our clinic. Lack of some prognostic factors, such as, presence of ascites, blood loss, operative time, perioperative morbidity, postoperative mortality can also be evaluated as another shortcoming of the study.

Conclusion

Lymphadenectomy may have a therapeutic value and be significantly associated with improved survival in advanced stage ovarian cancer patients. The effect of lymphadenectomy on PFS was only found in patients with early stage and advanced stage disease with >10 lymph node removed. In advanced stage patients, pelvic + paraaortic lymphadenectomy has more survival benefit compared to pelvic lymphadenectomy alone.

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