

COMMUNICATION

The impact of brain metastasis and other factors on overall survival in patients with metastatic non-small cell lung cancer

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Abstract

Brain metastases are common in metastatic non-small cell lung cancer (NSCLC) and portend poor outcomes, yet prognostic determinants—particularly whether brain metastases are present at diagnosis or develop during follow-up—remain incompletely characterized in driver-negative patients treated with first-line platinum-based doublet chemotherapy. This retrospective study evaluated prognostic factors affecting overall survival (OS) in patients with metastatic NSCLC who had brain metastases at diagnosis or developed them during follow-up and received first-line platinum-based doublet chemotherapy. A total of 136 epidermal growth factor receptor (EGFR)-, anaplastic lymphoma kinase (ALK)-, and c-ros oncogene-1 (ROS-1)-negative patients from a single center were included to identify key demographic, clinical, and treatment-related predictors of survival. Multivariate analysis showed that male sex (hazard ratio [HR]: 2.070), higher Eastern Cooperative Oncology Group (ECOG) performance status (HR: 1.438), presence of multiple metastatic sites (HR: 1.297), and lack of response to first-line chemotherapy (HR: 1.579) were independently associated with worse OS. Conversely, a higher number of chemotherapy cycles was a favorable prognostic factor (HR: 0.797). The timing of brain metastasis, whether present at diagnosis or occurring during follow-up, was not significantly associated with OS. Median OS for the entire cohort was 11.8 months. Females had longer survival than males (21.2 vs. 9.8 months), and patients receiving second-line therapy had improved survival compared with those who did not (24.2 vs. 8.3 months). Survival in this population appears to be primarily influenced by sex, performance status, metastatic burden, and treatment response rather than the timing of brain metastasis. These findings emphasize the importance of individualized treatment strategies, early response assessment, and access to subsequent therapy.

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1. Introduction

Lung cancer is the most common cause of cancer-related deaths worldwide in both men and women¹, and at the time of diagnosis, the vast majority of patients have locally advanced or metastatic disease.² Brain metastases develop in 30–40% of patients at

diagnosis and in approximately 50% during the course of the disease.³ Brain metastases are one of the most important factors determining the prognosis of the disease and significantly shorten survival. Despite advances in systemic chemotherapy and targeted therapies, survival in this patient group is generally limited.⁴

As with most metastatic cancers, the main goals of treatment in the metastatic stage of non-small cell lung cancer (NSCLC) are to prolong survival, achieve symptom control, and maintain quality of life. Platinum-based doublet chemotherapy regimens remain the standard first-line treatment option for patients without oncogenic driver mutations and who are not suitable for or have no access to immunotherapy.^{5,6}

Survival in metastatic NSCLC is highly heterogeneous and reflects the complex interplay of patient-, tumor-, and treatment-related determinants. Clinical characteristics, such as advanced age, comorbidities, and functional reserve, significantly influence treatment tolerance and overall prognosis, particularly in elderly populations where therapeutic decision-making often requires individualized balancing between efficacy and toxicity. In addition, tumor biology plays a central role in shaping outcomes; histological subtype, molecular alterations, and intrinsic tumor aggressiveness contribute to variability in disease progression and treatment responsiveness. The advent of immune checkpoint inhibitors has substantially altered the therapeutic landscape, demonstrating improved survival compared to conventional chemotherapy in selected patient populations and underscoring the importance of host-tumor immune interactions as a prognostic determinant. Moreover, demographic and biological factors, such as sex-related differences, have been associated with variations in treatment response and survival, potentially reflecting hormonal influences, molecular heterogeneity, and disparities in the immune microenvironment. Targetable oncogenic drivers further enhance prognostic stratification, as patients harboring actionable mutations may experience prolonged survival with effective targeted therapies, highlighting the importance of molecular profiling in metastatic disease. Nutritional and metabolic status, including body mass index and systemic inflammatory burden, have also emerged as clinically relevant prognostic indicators, likely reflecting both cancer-related cachexia and host inflammatory responses. Finally, population-based analyses using large registries have confirmed that survival outcomes are shaped by a combination of demographic features, disease burden, treatment accessibility, and competing risks, emphasizing the multifactorial nature of prognosis in metastatic NSCLC.⁷⁻¹²

Although numerous studies in the literature examine prognostic factors in metastatic NSCLC, a comprehensive analysis of these factors, specifically in patients who develop brain metastasis at diagnosis or during follow-up, is limited. The aim of this retrospective study is to present the demographic, clinical, pathological, and treatment-related prognostic factors affecting overall survival (OS) in patients with metastatic NSCLC, who are epidermal growth factor receptor (EGFR)/anaplastic lymphoma kinase (ALK)/c-ros oncogene-1 (ROS-1) negative, treated with platinum-based doublet chemotherapy, and who developed brain metastasis at diagnosis or during follow-up, to contribute to the literature.

2. Materials and methods

We retrospectively reviewed the files of lung cancer patients who were followed up and treated at the Van Yüzüncü Yıl University, Dursun Odabaşı Medical Center oncology clinic between 2012 and 2022. The study included patients over 18 years of age diagnosed with NSCLC who had metastatic disease at diagnosis, no EGFR, ALK, or ROS-1 mutations (all patients with non-squamous histology and adequate tumor tissue at our center after 2015 were included), received platinum-based doublet chemotherapy as first-line treatment, and had brain metastases at diagnosis or developed them during follow-up. Patients without a pathological diagnosis, with any EGFR, ALK, or ROS-1 mutations, receiving treatment other than platinum-based doublet chemotherapy, without brain metastasis, and with a second malignancy were excluded.

Demographic data (age, gender, smoking history), clinical characteristics (Eastern Cooperative Oncology Group [ECOG] performance status, height, weight, body mass index), pathological features (histological subtype, tumor localization), metastasis status (presence, site, and timing of distant organ metastases), and treatment-related data (administered chemotherapy regimens, treatment response, number of cycles received, administration of second-line therapy, and final status) were recorded.

Tumor staging was performed according to the Pathological Tumor, Node, Metastasis, 9th Edition.¹³ OS was defined as the time from the start of the first-line treatment to the date of death from any cause or the last follow-up date.

2.1. Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences software (SPSS 23.0, IBM Corp., USA). For descriptive statistics, continuous variables are presented as mean \pm standard deviation or median (minimum–maximum), and categorical variables

are presented as number (*n*) and percentage (%). The Kaplan–Meier method was used for OS analysis, and the log-rank test was applied to compare survival differences. Univariate and multivariate Cox proportional hazards regression models were used to identify prognostic factors affecting survival. Variables with $p < 0.05$ in the univariate analysis were included in the multivariate model. Results are reported as hazard ratios (HRs) and 95% confidence intervals (CIs). A two-sided $p < 0.05$ was considered statistically significant.

3. Results

A total of 136 patients were included in the study. The vast majority of patients were male (83.1%) and had a history of smoking (85.3%). The mean age at diagnosis was 56 ± 10 years. The distribution of ECOG performance status was as follows: 32.4% were ECOG 0, 21.3% were ECOG 1, 33.1% were ECOG 2, and 13.2% were ECOG 3.

In the pathological diagnosis distribution, squamous cell carcinoma (54.4%) was the most common subtype. Upon examination of lesion localization, the right upper lobe (39.0%) was the most frequently involved site, and overall, the right lung (64.7%) was more frequently involved than the left lung (35.3%). A single distant metastasis was present in 62.5% of patients, while multiple distant metastases were present in 37.5%.

The most frequently used first-line chemotherapy regimen was platinum + paclitaxel (41.2%). The response rate (complete + partial response) to first-line treatment was 45.6%, while progression occurred in 35.3% of patients. The largest proportion of patients (46.9%) received four cycles of chemotherapy. Second-line therapy was administered to only 41.9% of patients. At the end of follow-up, 80.1% of patients were deceased, while 19.9% survived (Table 1).

Univariate analysis examining factors determining OS identified several statistically significant factors. Accordingly, male gender (HR: 1.853, 95% CI: 1.087–3.159, $p = 0.023$), high ECOG performance score (HR: 2.096, 95% CI: 1.710–2.568, $p < 0.001$), presence of multiple distant metastases (HR: 1.272, 95% CI: 1.050–1.542, $p = 0.014$), presence of bone metastasis (HR: 1.333, 95% CI: 1.031–1.723, $p = 0.028$), and non-response to first-line chemotherapy (HR: 2.173, 95% CI: 1.769–2.670, $p < 0.001$) were significantly associated with poor prognosis. The first-line chemotherapy regimen (HR: 0.723, 95% CI: 0.596–0.876, $p = 0.001$) (among the chemotherapy regimens, the platinum + pemetrexed regimen was associated with a statistically significantly higher survival compared to the other three regimens), receiving a higher number of chemotherapy cycles (HR: 0.683, 95% CI: 0.590–0.790, p

< 0.001), and administration of second-line therapy (HR: 0.376, 95% CI: 0.249–0.567, $p < 0.001$) were favorable prognostic factors.

Multivariate Cox regression analysis showed that male gender (HR: 2.070, 95% CI: 1.168–3.667, $p = 0.013$), high ECOG score (HR: 1.438, 95% CI: 1.111–1.861, $p = 0.006$), presence of multiple metastases (HR: 1.297, 95% CI: 1.059–1.588, $p = 0.012$), and non-response to first-line treatment (HR: 1.579, 95% CI: 1.214–2.053, $p = 0.001$) remained independent poor prognostic factors. A higher number of cycles received (HR: 0.797, 95% CI: 0.688–0.924, $p = 0.003$) was identified as an independent predictor of favorable prognosis (Table 2).

The median survival for all patients in the study was 11.8 months (95% CI: 7.9–15.7). Survival differed according to gender. The median survival in female patients was 21.2 months (95% CI: 9.9–32.5), whereas it was 9.8 months (95% CI: 7.6–12.0) in male patients. The log-rank analysis showed a statistically significant difference in survival between genders ($p = 0.021$) (Figure 1). Analysis according to ECOG performance status revealed significant differences between the groups ($p < 0.001$). In pairwise comparisons, the ECOG 0 group had significantly longer survival compared to the ECOG 1, 2, and 3 groups ($p < 0.001$ for all comparisons). Additionally, the differences between ECOG 1 and ECOG 3 ($p = 0.014$) and between ECOG 2 and ECOG 3 ($p = 0.018$) were also statistically significant. In contrast, no difference in survival was observed between the ECOG 1 and ECOG 2 groups ($p = 0.276$) (Figure 1). These findings demonstrate that an increasing ECOG score is an adverse prognostic factor for survival.

Metastatic burden at diagnosis was also identified as an important factor affecting survival. The median survival in patients with a single metastatic site was 14.9 months (95% CI: 8.8–21.0), whereas it was 8.8 months (95% CI: 6.7–10.9) in patients with multiple metastases. The log-rank test showed that this difference was statistically significant ($p = 0.013$) (Figure 1). When treatment-related factors were evaluated, survival was significantly longer in patients who received second-line therapy. The median survival was 8.3 months (95% CI: 6.4–10.1) in patients who did not receive second-line therapy, while it was 24.2 months (95% CI: 17.3–31.0) in those who did ($p < 0.001$) (Figure 1). Response to first-line treatment also strongly influenced survival. The median survival was 10.6 months (95% CI: 7.9–13.3) in patients who did not respond, while it was 42.5 months (95% CI: not estimable–91.1) in patients who did respond. The difference between the two groups was statistically significant by log-rank analysis ($p < 0.001$) (Figure 1).

No statistically significant difference in survival was found between patients with brain metastasis at diagnosis and those who developed brain metastasis during follow-up.

Table 1. Clinical demographic and pathological characteristics of patients

Demographic and characteristics	Category	Min-max	Median	Mean \pm SD/n (%)
Gender	Woman			23 (16.9)
	Male			113 (83.1)
Age at diagnosis (year)		21–81	56	56 \pm 10
Smoking status	No			20 (14.7)
	Yes			116 (85.3)
ECOG	0			44 (32.4)
	1			29 (21.3)
	2			45 (33.1)
	3			18 (13.2)
Height (cm)		140–186	170	168 \pm 8
Weight (kg)		48–100	67	68 \pm 11
BMI (kg/m ²)		16.0–36.7	24.0	24.1 \pm 4.0
Pathological diagnosis	NOS			31 (22.8)
	Non-squamous			31 (22.8)
	Squamous			74 (54.4)
	Right lower lobe			25 (18.4)
Tumor location	Right upper lobe			53 (39.0)
	Left lower lobe			21 (15.4)
	Left upper lobe			27 (19.9)
	Right middle lobe			10 (7.4)
Laterality	Right			88 (64.7)
	Left			48 (35.3)
Pleural effusion	No			116 (85.3)
	Yes			19 (14.0)
Distant metastasis	Single			85 (62.5)
	Multiple			51 (37.5)
Brain metastasis	At diagnosis			86 (63.2)
	During follow-up			50 (36.8)
	None			109 (80.1)
Contralateral lung metastasis	At diagnosis			18 (13.2)
	During follow-up			9 (6.6)
	None			107 (78.7)
Liver metastasis	At diagnosis			19 (14.0)
	During follow-up			10 (7.4)

(Cont'd...)

Table 1. (Continued)

Demographic and characteristics	Category	Min-max	Median	Mean \pm SD/n (%)
Adrenal metastasis	None			94 (69.1)
	At diagnosis			31 (22.8)
	During follow-up			11 (8.1)
Bone metastasis	None			70 (51.5)
	At diagnosis			53 (39.0)
	During follow-up			13 (9.6)
Pleural metastasis	None			124 (91.2)
	At diagnosis			10 (7.4)
	During follow-up			2 (1.5)
1st line treatment regimen	Platinum + paclitaxel			56 (41.2)
	Platinum + gemcitabine			48 (35.3)
	Platinum + vinorelbine			15 (11.0)
	Platinum + pemetrexed			17 (12.5)
	Complete			8 (5.9)
Best response to 1st line	Partial			54 (39.7)
	Stable			19 (14.0)
	Progress			48 (35.3)
	1			8 (6.2)
	2			12 (9.2)
Number of cycles	3			13 (10.0)
	4			61 (46.9)
	5			4 (3.1)
	6			29 (22.3)
	8			1 (0.8)
Progression	12			1 (0.8)
	15			1 (0.8)
	No			10 (8.1)
	Yes			114 (91.9)
2nd line treatment	No			79 (58.1)
	Yes			57 (41.9)
Final status	Alive			27 (19.9)
	Dead			109 (80.1)

Abbreviations: BMI: Body mass index; ECOG: Eastern Cooperative Oncology Group; NOS: Not otherwise specified; SD: Standard deviation.

Table 2. Univariate and multivariate analysis for overall survival

Variables	Univariate analysis				Multivariate analysis			
	HR	95% CI for HR		<i>p</i>	HR	95% CI for HR		<i>p</i>
		Lower	Upper			Lower	Upper	
Gender (ref. female)	1.853	1.087	3.159	0.023*	2.070	1.168	3.667	0.013*
Age at diagnosis	1.005	0.987	1.023	0.603	NR	NR	NR	NR
BMI	0.982	0.922	1.046	0.573	NR	NR	NR	NR
Cigarette	1.669	0.950	2.933	0.075	NR	NR	NR	NR
ECOG	2.096	1.710	2.568	<i>p</i> < 0.001*	1.438	1.111	1.861	0.006*
Pathological diagnosis	0.764	0.611	0.957	0.019*	NR	NR	NR	NR
Anatomical localization	0.999	0.849	1.175	0.989	NR	NR	NR	NR
Distant metastasis (ref: single)	1.272	1.050	1.542	0.014*	1.297	1.059	1.588	0.012*
Pleural effusion (ref: no)	1.019	0.629	1.650	0.940	NR	NR	NR	NR
Brain metastasis (ref: at follow-up)	1.080	0.731	1.596	0.699	NR	NR	NR	NR
Contralateral lung metastasis (ref: no)	0.782	0.543	1.128	0.188	NR	NR	NR	NR
Liver metastasis (ref: no)	0.970	0.726	1.296	0.837	NR	NR	NR	NR
Adrenal metastasis (ref: no)	1.155	0.877	1.521	0.304	NR	NR	NR	NR
Bone metastasis (ref: no)	1.333	1.031	1.723	0.028*	NR	NR	NR	NR
Pleural metastasis (ref: no)	1.192	0.682	2.083	0.538	NR	NR	NR	NR
1st line chemotherapy regimen	0.723	0.596	0.876	0.001*	NR	NR	NR	NR
Non-response to 1st line treatment (ref: response)	2.173	1.769	2.670	<i>p</i> < 0.001*	1.579	1.214	2.053	0.001*
Number of chemotherapy cycles	0.683	0.590	0.790	<i>p</i> < 0.001*	0.797	0.688	0.924	0.003*
Progression after 1st line (ref: no)	1.275	0.583	2.784	0.543	NR	NR	NR	NR
2nd line treatment (ref: no)	0.376	0.249	0.567	<i>p</i> < 0.001*	NR	NR	NR	NR

Notes: **p* < 0.05; Only variables with a *p*-value < 0.05 in the univariate analysis were included in the multivariate Cox regression model; multivariate results are shown for variables retained in the final model; other entered variables are marked NR (not retained).

Abbreviations: BMI: Body mass index; ECOG: Eastern Cooperative Oncology Group; CI: Confidence interval; HR: Hazard ratio; Ref: Reference category.

4. Discussion

Our study showed that male gender, high ECOG performance score, presence of multiple metastases, and non-response to first-line treatment were independent poor prognostic factors. Receiving a higher number of chemotherapy cycles was independently associated with longer OS. No association was found between survival and having brain metastasis at diagnosis or developing it during follow-up. The median OS of 11.8 months observed in our cohort reflects outcomes from the platinum-based chemotherapy era. In the current era of immunotherapy and targeted treatments, OS outcomes have substantially improved.

Sex-related differences have been associated with prognosis in several cancers. In our study, female gender was associated with longer survival (21.2 months vs. 9.8 months). The factors underlying the more favorable prognosis observed in women with lung cancer are multifactorial and can be attributed to a combination of biological, molecular, and clinical differences.

Historically, lung cancer in women has been shown to be more frequently associated with adenocarcinoma histology, earlier stage at diagnosis, and a more favorable response to systemic therapies. Recent molecular and biological evidence further supports these observations, demonstrating a higher prevalence of actionable driver mutations—particularly EGFR mutations—in female patients, along with less aggressive tumor biology and a tumor immune microenvironment that appears more responsive to treatment. In addition, estrogen receptor-mediated signaling has been suggested to exert regulatory effects on tumor proliferation, apoptosis, and immune responses, thereby potentially modulating both tumor development and therapeutic efficacy in women.^{14,15}

The ECOG performance score is a strong prognostic marker for most metastatic cancers. In our study, survival was significantly longer in patients with ECOG 0, while it was markedly shortened in those with ECOG ≥ 1 . A previous study has also reported that the ECOG score is one of the most important indicators of treatment response

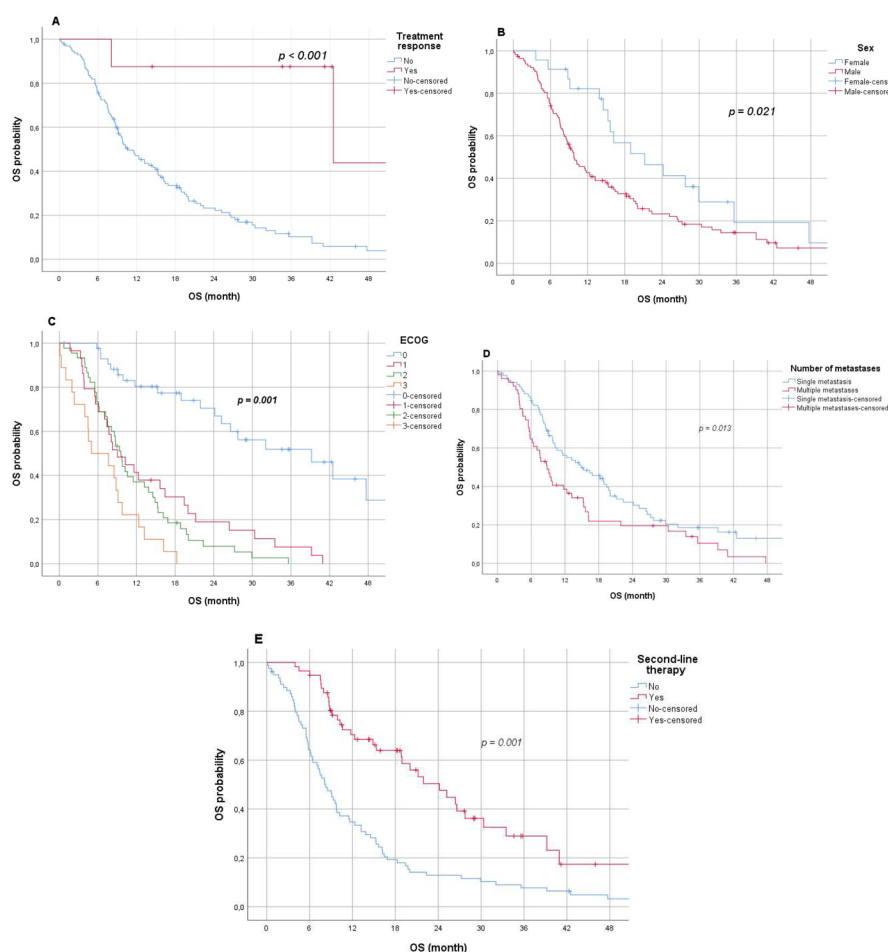


Figure 1. Kaplan–Meier analysis of overall survival (OS) stratified by (A) treatment response, (B) gender, (C) Eastern Cooperative Oncology Group (ECOG) performance score, (D) metastatic burden, and (E) second-line therapy

and survival in metastatic NSCLC patients.¹⁶

The number of metastases is a significant prognostic factor in metastatic disease. In our study, survival was considerably lower in patients with multiple metastatic sites compared to those with a single metastasis (8.8 months vs. 14.9 months). This difference was statistically significant and identified as an independent poor prognostic factor in multivariate analysis (HR: 1.297, $p = 0.012$). The literature has shown that survival can be prolonged with more aggressive local treatments (radiotherapy, surgery) in oligometastatic disease.¹⁷

Treatment response is an important factor directly affecting survival. In our study, we found that the risk increased 1.579-fold ($p = 0.001$) in patients who did not respond to first-line chemotherapy. Various studies in the literature have shown that survival is longer in responding patients¹⁸, and since responding patients received more cycles, survival was higher in patients who received more cycles, consistent with this finding.

Furthermore, survival was significantly longer in patients who received second-line therapy (24.2 months vs. 8.3 months). This indicates that second-line treatment options improve survival in this patient group¹⁹ and should be offered to patients with adequate performance status.

One of the strengths of the study is the evaluation of a homogeneous patient group (EGFR/ALK/ROS-1 negative, receiving platinum-based chemotherapy). However, the retrospective single-center design, the lack of detailed data regarding the number of brain metastases and brain-directed treatments (such as surgery or radiotherapy), and the absence of immunotherapy in the treatment landscape constitute important limitations of this study.

5. Conclusion

In conclusion, our findings confirm that male gender, high ECOG score, multiple metastases, and non-response to first-line chemotherapy are adverse prognostic factors in metastatic NSCLC with brain metastases, while a higher number of chemotherapy cycles and the administration of second-line therapy result in longer survival. This information underscores the importance of personalized treatment strategies, early response assessment, and access to subsequent lines of therapy to optimize outcomes in this challenging population. Future prospective studies, including those evaluating immunotherapy and novel agents, are required to refine these prognostic models.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: All authors

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Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval for the study was obtained from the Van Yüzüncü Yıl University Non-Interventional Clinical Research Ethics Committee (Approval No: 2023/09-23, Date: September 18, 2023). The ethics committee approved the study protocol, including patient selection, retrospective data collection from hospital records, and statistical analysis of anonymized clinical data. Due to the retrospective design of the study and the use of anonymized patient data, the requirement for written informed consent was waived by the ethics committee. Patient confidentiality and data privacy were strictly maintained throughout the study.

Consent for publication

Not applicable.

Availability of data

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request and with permission of the institutional ethics committee.

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