

## Risk factors affecting survival after brain metastases from non–small cell lung carcinoma: a follow-up study of 70 patients

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**Object.** The authors present their experience with the treatment of brain metastases from non–small cell lung carcinoma (NSCLC).

**Methods.** A retrospective review was conducted in which records from 74 patients treated at the authors' institution between 1994 and 1999 were assessed. Survival and functional outcome were reviewed relative to individual patient variables. The median survival time was 12.9 months, with 1-, 2-, and 5-year survival milestones reached by 52.2%, 30.7%, and 18.1% of patients, respectively. Patients were stratified into groups composed of those with synchronous brain metastases (tumors diagnosed within 3 months of NSCLC) and metachronous brain metastases (tumors diagnosed 3 months after NSCLC). The median survival time and 5-year survival rate were 18 months and 28.9% for metachronous, compared with 9.9 months and 0% for synchronous brain metastases. In univariate analyses, the stage of brain metastases, an initial Karnofsky Performance Scale (KPS) score of 90 or less, and conservative therapy for NSCLC were associated with worse outcomes ( $p < 0.05$ ). In analyses in which tumors were stratified by synchronous compared with metachronous brain metastases, a preoperative KPS score of 90 or less and radiation therapy (RT) alone for brain metastases were associated with worse outcomes in patients with metachronous brain metastases but not with synchronous tumors ( $p < 0.05$ ). When stratified by preoperative KPS score, the synchronous brain metastases stage or treatment of brain metastases with RT alone were associated with worse outcome in patients with KPS scores of 100, but had no discernible effect on patients with KPS scores of 90 or less ( $p < 0.05$ ).

**Conclusions.** The tumor stage and preoperative KPS score were significantly associated with survival. Craniotomy plus RT significantly improved the prognosis in patients with metachronous brain metastases or those with a preoperative KPS score of 100.

**KEY WORDS** • metastasis • metachronous tumor • non–small cell lung carcinoma • synchronous tumor

THE incidence of brain metastases from lung cancer (Stage IV) at initial staging ranges from 10 to 18%,<sup>2,11,20</sup> with a cumulative incidence of more than 50% at 2 years.<sup>15</sup> In general, evidence of brain metastases has been reported in autopsy series<sup>6,9,14</sup> in 30 to 80% of patients with lung cancer. After diagnosis and thoracotomy for NSCLC, 12-month evaluations with computerized tomography and magnetic resonance imaging revealed evidence of brain metastases in 7.1% and 6.8% of patients, respectively.<sup>33</sup> After complete resection of primary lung tumors, the occurrence of brain metastases has been documented to be as low as 1 to 15%.<sup>8</sup> Once brain metastases are diagnosed, the median survival time without treatment ranges from 1 to 6 months.<sup>6,8,9</sup> In fact, survival of 10 years or longer has been cited in anecdotal reports on 16 patients treated with aggressive therapy.<sup>26</sup>

Those with solitary brain metastases from lung cancer are recognized as a subgroup of patients who have benefited from an aggressive surgical approach.<sup>4,21,22,27</sup> Combined surgical excision of both the primary lung cancer and brain metastasis, followed by WBRT, significantly prolongs survival.<sup>17,21,22</sup> In this study, we present a cohort of patients treated at our institution in whom brain metastases from NSCLC were diagnosed. Patients were stratified into two groups: those with synchronous brain metastases (tumors diagnosed within 3 months of NSCLC [Group 1]) and those with metachronous brain metastases (tumors diagnosed 3 months or more after NSCLC [Group 2]). We determined overall survival and risk factors relative to the diagnosis of NSCLC and brain metastases.

### Clinical Material and Methods

We reviewed the records of 74 patients with histologically confirmed NSCLC brain metastases treated at the Hospital of the University of Pennsylvania between March

*Abbreviations used in this paper:* CI = confidence interval; KPS = Karnofsky Performance Scale; LCC = large cell carcinoma; NSCLC = non–small cell lung carcinoma; RT = radiation therapy; SCC = squamous cell carcinoma; WBRT = whole-brain RT.

TABLE 1  
Patient characteristics stratified into presentation with SBM or MBM\*

Factor	No. of Patients (%)		
	Total	MBM	SBM
no. of patients	70 (100)	34 (48.6)	36 (51.4)
brain treatment			
palliative care	3 (4.3)	0 (0)	3 (8.3)
craniotomy	6 (8.5)	2 (5.9)	4 (11.1)
craniotomy + RT	44 (62.9)	23 (67.6)	21 (58.3)
RT	17 (24.3)	9 (26.5)	8 (22.2)
pathological finding			
AC	43 (61.4)	20 (58.8)	23 (63.9)
SCC	7 (10.0)	4 (11.8)	3 (8.3)
LCC	20 (28.6)	10 (29.4)	10 (27.8)
sex			
female	39 (55.7)	18 (53)	21 (58.3)
male	31 (44.3)	16 (47)	15 (41.7)
age			
<60 yrs	35 (50)	16 (47)	19 (52.8)
>60 yrs	35 (50)	18 (53)	17 (47.2)
tumor location			
infratentorial	10 (14.3)	4 (11.8)	6 (16.7)
supratentorial	60 (85.7)	30 (88.2)	30 (83.3)
outcome			
survival	25 (35.7)	15 (44.1)	10 (27.8)
death	45 (64.2)	19 (55.9)	26 (72.2)
metastases			
single	47 (67.1)	25 (73.5)	22 (61)
multiple	23 (32.9)	9 (26.5)	14 (39)
recurrence			
no	52 (74)	22 (64.7)	30 (83.3)
yes	18 (26)	12 (35.3)	6 (16.7)
KPS score			
≤90	51 (73)	25 (73.5)	26 (72.2)
100	19 (27)	9 (26.5)	10 (27.8)
lung treatment			
no surgery	44 (62.9)	29 (85.3)	15 (41.7)
thoracotomy	26 (37.1)	5 (14.7)	21 (58.3)

\* AC = adenocarcinoma; MBM = metachronous brain metastasis; SBM = synchronous brain metastasis.

1994 and October 1999. Four patients were unavailable for follow-up review and were excluded from the study. For the remaining 70 patients, data were collected for basic demographics, lung cancer stage and treatment, brain metastasis and treatment, and functional outcome, which was assessed by calculating the preoperative and follow-up KPS scores. Lung treatment was stratified into thoracotomy with or without RT or chemotherapy (26 patients), compared with no surgery with or without RT or chemotherapy (44 patients). As shown in Table 1, treatment of brain metastases consisted of supportive care (three patients), craniotomy alone (six patients), craniotomy plus RT (44 patients), and RT alone (17 patients).

Radiation therapy for brain metastases included WBRT, radiosurgery, or both. Whole-brain radiation therapy consisted of doses ranging from 3000 to 5000 cGy over 10 fractions, and radiosurgery consisted of a single boost ranging from 1500 to 2400 cGy. No brain lesions were treated with chemotherapeutic agents. Functional outcome was assessed by taking into account the length of survival after diagnosis of NSCLC and brain metastases, as well as KPS scores assessed preoperatively and postoperatively

TABLE 2  
Median survival times and 1-, 2-, and 5-year survival rates for patients with brain metastases\*

Group	No. of Patients	Median Survival Time (mos)	Rates of Survival (%)		
			1-Year	2-Year	5-Year
all patients	70	12.9	52.2	30.7	18.1
95% CI		5.2–36.9	41.0–66.4	20.4–46	9.3–35.3
patients w/ MBM	34	18.0	94.1	84.9	28.9
95% CI		11.3†	86.5–100	73.5–98	15.6–53.5
patients w/ SBM	36	9.9	39.7	25.8	0
95% CI		3.6–41.5	26–60.8	14.1–58.4	NA

\* NA = not applicable.

† Twenty-seven percent were alive after last follow up at 77 months.

when possible at 1-month, 3-month, 6-month, and 1-year follow-up examinations.

### Statistical Analysis

Survival from the date of diagnosis of either NSCLC or brain metastases was estimated using the Kaplan–Meier method, with Greenwood estimates of the standard deviation and 95% CIs based on log survival.<sup>13</sup> For all statistical analyses we used S-PLUS version 3.4 software (Mathsoft, Cambridge, MA). To assess risk factors affecting survival, Cox proportional hazards models were constructed, with individual variables initially and then for stratified models.<sup>5,12</sup> Graphics techniques were used to assess the assumption of proportional hazards, and all tests of the hypotheses were conducted at a probability value of less than 0.05 (two-tailed). Risk factors are presented in terms of 95% CIs relative to a baseline group that is assigned a risk of 1. Note that 95% CIs that do not cover the number 1 are equivalent to a hypothesis test with a probability value of less than 0.05.

### Results

We reviewed the cases of 70 patients (31 men and 39 women) who ranged in age from 32 to 82 years (mean age 59 years). At the time of data collection, 45 patients (64%) had died and 25 (36%) were alive. In all, there were 140 hemispheric metastases with 118 primary lesions (84%) overall, and 22 (16%) recurrent lesions in 18 patients (26%). Forty-seven patients presented with one lesion and 23 presented with multiple lesions. Of the patients with multiple lesions, 10 presented with two lesions, six presented with three lesions, three presented with four lesions, three presented with five lesions, and one presented with six lesions. For patients with metachronous brain metastases, the interval between diagnoses of NSCLC and brain metastasis ranged from 3 to 104 months, with a median interval of 18 months. For recurrences, 14 patients presented with a single lesion and four presented with two lesions. The interval from the diagnosis of the first brain metastases to a recurrent lesion ranged from 3 to 28 months, with a median time to recurrence of 8 months.

### Overall Survival

Median follow-up duration was 18 months, and the

## Risk factors affecting survival after brain metastases

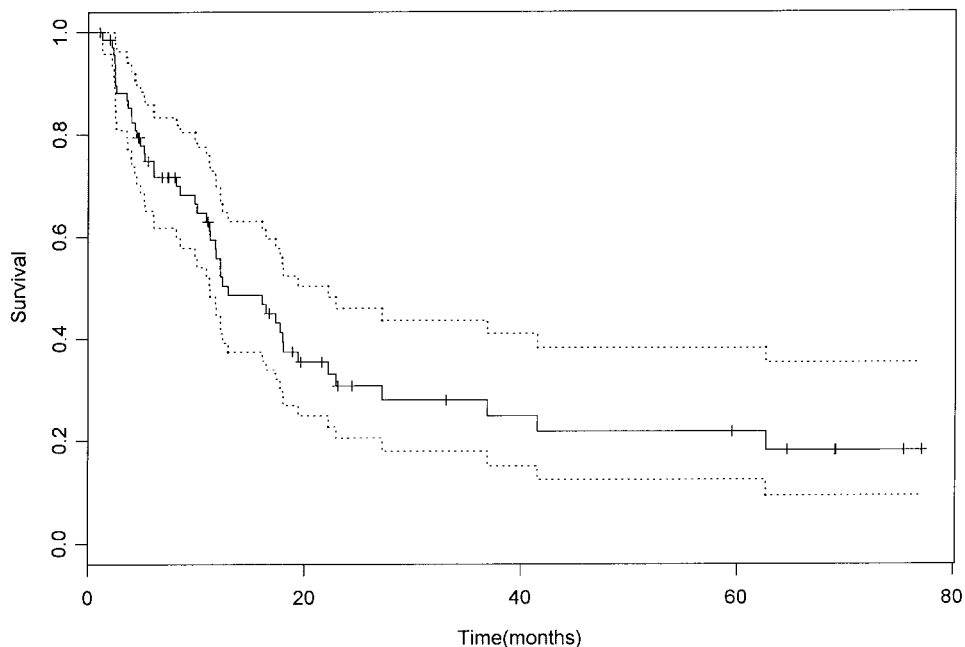


FIG. 1. Graph showing Kaplan–Meier survival curves with 95% CIs in patients after the diagnosis of brain metastases.

overall median survival time was 12.9 months. The 1-, 2-, and 5-year survival rates were 52.2%, 30.7%, and 18.1%, respectively (Table 2 and Fig. 1). Of particular interest are the long-term survivors: six patients (8.6%) survived for at least 5 years following diagnosis of brain metastases.

### Univariate Models

The risk factors of tumor stage and KPS score were significantly associated with survival (Table 3). Once diagnosed with brain metastases, patients with synchronous disease still had a 1.44-fold increased risk of death compared with the patients with metachronous brain metastases ( $p < 0.05$ ). Patients who entered the study with a KPS score of 100 had a 0.66-fold reduced risk of death compared with patients with a KPS score of 90 or lower ( $p < 0.05$ ). There were no significant associations between survival and the number of recurrent brain metastases.

### Synchronous Compared With Metachronous Brain Metastases

The number of patients receiving palliative care or craniotomy alone for brain metastases was small, and these patients therefore were omitted from the stratified analyses to prevent unstable results (Table 1). Also, the patients who had SCC were omitted from the final analysis because of their small numbers. Because of its importance for survival following NSCLC, we stratified the tumor stage into synchronous compared with metachronous brain metastases and further considered risk factors affecting survival.

When stratified by metachronous compared with synchronous brain metastases, the median survival time and 5-year survival rate were 18 months and 28.9% compared to 9.9 months and 0%, respectively (Table 1). There were no other risk factors found in patients with synchronous

TABLE 3  
Risk factors affecting survival, stratified by diagnosis of brain metastases\*

Risk Factor	Relative Risk (95% CI)
brain treatment	
palliative	1.12 (0.32–1.38)
craniotomy alone	0.81 (0.39–1.65)
RT + craniotomy	1.00
RT alone	1.15 (0.68–1.94)
stage	
MBM	1.00
SBM	1.44 (1.06–1.95)†
pathological finding	
AC	1.00
LCC	1.07 (0.84–1.37)
sex	
female	1.00
male	0.97 (0.72–1.30)
age	
<60 yrs	1.00
>60 yrs	1.12 (0.83–1.50)
no. of metastases	
1	1.00
>1	1.11 (0.82–1.50)
lung treatment	
no surgery	1.23 (0.90–1.75)
thoracotomy	1.00
KPS score	
≤90	1.00
100	0.66 (0.45–0.97)†
recurrence	
no	1.00
yes	0.75 (0.39–1.44)

\* Based on the Cox proportional hazards models.

† Significant difference at  $p < 0.05$ .

TABLE 4  
Risk factors affecting survival after diagnosis of NSCLC, stratified into SBM or MBM\*

Risk Factor & Level	SBM		MBM	
	No.	Relative Risk (95% CI)	No.	Relative Risk (95% CI)
pathological finding				
AC	18	1.00	18	1.00
LCC	8	0.88 (0.62–1.25)	10	1.03 (0.66–1.61)
KPS score				
≤90	20	1.00	24	1.00
100	9	0.95 (0.59–1.55)	8	0.37 (0.17–0.79)†
treatment				
craniotomy + RT	21	1.00	23	1.00
RT alone	8	0.93 (0.59–1.49)	9	1.70 (1.40–2.78)†

\* Cases were stratified on entry into the study. Patients receiving palliative care or craniotomy only were excluded, as were patients with a pathologically confirmed diagnosis of SCC.

† Significant difference at  $p < 0.05$ .

brain metastases that were statistically associated with differences in survival. For patients with metachronous brain metastases, the preoperative KPS score and treatment of brain metastases were significantly associated with length of survival (Table 4). Patients with a preoperative KPS score of 100 had a 0.37-fold decreased risk of death compared with the patients with a KPS score of 90 or less ( $p < 0.05$ ). In the patients who were treated with RT only there was a 1.7-fold increased risk of death compared with the patients who underwent craniotomy plus RT ( $p < 0.05$ ).

#### Karnofsky Performance Scale Score

In our analyses of KPS scores, patients were divided into two groups: those with a score of 100 compared with those with a score of 90 or less (Table 5). We also considered using three categories corresponding to a KPS score of 100, 90, and 80 or less. In general, however, we found that patients with a KPS score of 90 had an intermediate risk of treatment failure compared with those whose KPS score was either 100 or 80 or less, but that the risk was not statistically different from that in patients with KPS scores of 80 or less. We found that neither treatment for brain metastases nor the stage of the disease was a significant risk factor for patients with KPS scores of 90 compared with those with KPS scores of 80 or less. In this study, there is enough statistical power to detect a decreased risk between patients with KPS scores of 100 and other patients. We may have insufficient statistical power to detect a decreased risk between patients with KPS scores of 90 and other patients, however, if that risk is small. In other words, a clinically important change in risk may exist for patients with KPS scores of 90, but because of the number of patients enrolled in our study we may be unable to detect statistically significant effects. Therefore, the KPS score was stratified into patients with scores of 100 and those with scores of 90 or less (Fig. 2).

For patients with KPS scores of 90 or less there were no statistically significant associations with any of the risk factors in Table 3. For the 17 patients with preoperative KPS scores of 100, however, the stage of the tumor, treat-

TABLE 5  
Risk factors after diagnosis of brain metastases, stratified by preoperative KPS score\*

Risk Factor & Level	KPS Score 100		KPS Score ≤90	
	No.	Relative Risk (95% CI)	No.	Relative Risk (95% CI)
stage				
MBM	8	1.00	24	1.00
SBM	9	2.68 (1.19–6.02)†	20	1.12 (0.79–1.60)
treatment				
craniotomy + RT	12	1.00	37	1.00
RT alone	5	2.61 (1.11–6.16)†	12	0.96 (0.64–1.42)
pathological finding				
AC	13	1.00	23	1.00
LCC	4	2.53 (1.00–6.42)†	14	0.94 (0.71–1.24)

\* Patients receiving palliative care or craniotomy only were excluded, as were patients with a pathologically confirmed diagnosis of SCC.

† Significant difference at  $p < 0.05$ .

ment for brain metastases, and pathological findings were significantly associated with survival. Patients who presented with synchronous brain metastases, were treated with RT alone, or had a diagnosis of LCC on pathological studies had a 2.7-fold, 2.6-fold, and 2.5-fold increased risk of death, respectively. Particularly with respect to pathological studies, these findings are tentative because of the small number of patients in the LCC stratum (four patients).

Last, KPS scores were analyzed in patients preoperatively and in those who survived at 1-, 3-, 6-, and 12-month intervals following surgery (Table 6). The median preoperative and 1-month postoperative KPS scores were both 90, and the KPS scores at the 3-, 6-, and 12-month intervals remained relatively constant at 80, meaning that the patients who survived did so with a good quality of life.

#### Discussion

In our cohort of patients one of the primary factors affecting survival was the stage of the disease at presentation. We found that compared with patients with metachronous brain metastases, those with synchronous brain metastases had aggressive disease that shortened their survival. Five years after diagnosis of brain metastases, 28.9% of patients with metachronous brain metastases were alive compared with 0% of those with synchronous brain metastases. Treatment of brain metastases with craniotomy plus RT was superior to RT alone in patients with metachronous brain metastases, whereas there was no significant benefit in patients with synchronous brain metastases. In early reports the synchronous onset of brain metastases with lung cancer was considered an adverse prognostic indicator,<sup>17,28</sup> whereas in others no significant difference was found in survival.<sup>10,23,30</sup> In patients with metachronous brain metastases, it has been shown that a longer time between the diagnosis of NSCLC and craniotomy for brain metastases improves long-term survival.<sup>27</sup>

The other primary factor affecting survival was the preoperative KPS score, with a significant dichotomy emerging when patients were stratified by this score. Patients with preoperative KPS scores of 100 benefited from cra-

## Risk factors affecting survival after brain metastases

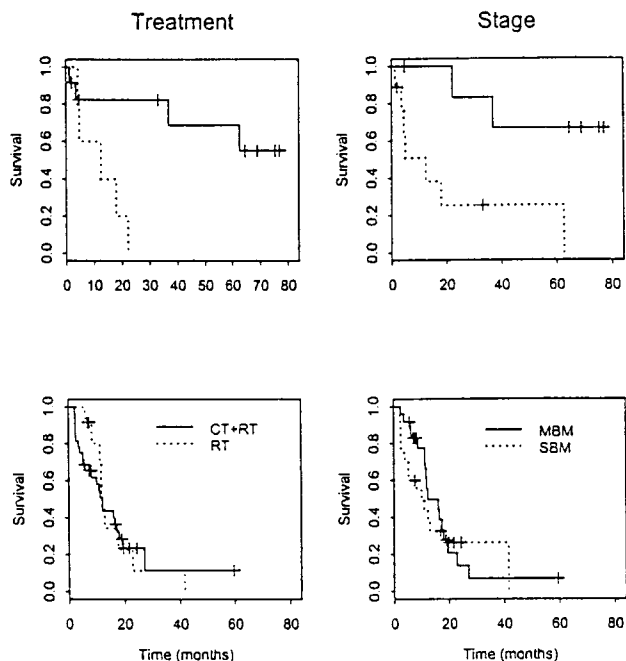


FIG. 2. Graphs showing Kaplan–Meier survival curves stratified by treatment, tumor stage, and preoperative KPS score following diagnosis of brain metastases. *Top row:* KPS scores = 100; *bottom row:* KPS score = 90 or less. CT = craniotomy.

niotomy plus RT compared with RT alone, and had a better prognosis overall than the patients with KPS scores of 90 or less. For patients with metachronous brain metastases and KPS scores of 100, however, treatment of brain metastases with craniotomy plus RT, and a pathological finding of adenocarcinoma, there was a significant improvement in survival (Table 5).

In some reports it has been shown that patients with solitary brain metastases from NSCLC who underwent both thoracotomy and craniotomy have an overall 5-year survival rate of 30%.<sup>16</sup> We found that the importance of tumor stage and initial KPS score was reflected in the long-term survivors. All three patients who survived at least 8 years after diagnosis of NSCLC, and five of six patients who survived at least 5 years after diagnosis of brain metastasis had KPS scores of 100 and a tumor stage of metachronous brain metastases. In terms of functional outcome, a median KPS score of 80 was sustained at 3-, 6-, and 12-month follow-up intervals, thus showing that patients perform at a high level 1 year after surgery.

An interval of more than 12 months between lung resection and craniotomy significantly affected both survival and the disease-free interval.<sup>16</sup> In a study similar to ours, the median survival time was 7 months after treatment with craniotomy, WBRT, chemotherapy, or with some combination of these modalities.<sup>4</sup> The number of brain metastases and treatment with craniotomy or WBRT were factors found to affect survival significantly, although there was no significant association between survival and age, sex, histological tumor type, location of brain metastases, or, unlike in our study, general performance scores.

The 5-year survival rate of patients with resectable

TABLE 6  
Summary of median KPS scores for all patients before and after treatment

Factor	KPS Score (95% CI)				
	Preop	1-Mo	3-Mo	6-Mo	12-Mo
KPS score	90 (80–100)	90 (80–90)	80 (70–90)	80 (70–90)	80 (70–90)
no. of patients	69	70	70	45	30

NSCLC and a single brain metastasis has been reported to be anywhere from 12.5%<sup>32</sup> to as high as 30%.<sup>16</sup> For those patients who underwent craniotomy plus adjuvant therapy, the median survival time ranged from 8 to 19 months.<sup>3,7,16,28,29,31,32</sup> In patients with metachronous brain metastases, the median survival time reportedly ranges from 9 to 14 months.<sup>1,3,18,19</sup> Survival rates for patients with brain metastases from NSCLC range from 37 to 55% at 1 year<sup>3,24,25,28</sup> and from 14 to 27% at 2 years.<sup>3,25,28</sup> Despite the fact that we evaluated survival among all patients who presented to our institution over a 5-year period, and not a particular subgroup, our results were comparable to those previously reported in the literature.

One limitation of this study is that its purpose was to follow retrospectively the natural history of brain metastases. Because this was a retrospective review rather than a prospective, randomized trial, there are obvious selection biases in our treatment regimen for each patient. Therefore, these results should be interpreted with caution in terms of recommendations for general management decisions in patients with synchronous or metachronous brain metastases. Another limitation of this study is that we have analyzed the cohort of patients as one group rather than focusing on a subgroup such as those with solitary metastases. We did compare single and multiple brain metastases, and we also compared solitary and recurrent brain metastases; however, we found no significant differences in survival among these groups. Another limitation is that we did not account for progression of systemic disease and whether the cause of death was from primary or secondary lesions. Although our study has these limitations, our main objective was to characterize a typical cohort of patients who present to a neurosurgical service and to characterize their outcome.

### Conclusions

Our median survival results after the diagnosis of brain metastases are in agreement with previous reports, even though we did not study a subgroup of patients who typically have better rates of survival. In this study, the tumor stage and preoperative KPS scores were important predictors for survival. For patients with KPS scores of 100, our results support previous claims that patients with metachronous brain metastases have longer survival compared with patients with synchronous brain metastases. In patients with a preoperative KPS score of 90 or less, however, there is no significant difference in patients with metachronous brain metastases or synchronous brain metastases, or in the survival rates of these patients after treatment with craniotomy plus RT or RT alone.

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