Original Article

Novel biologic factors correlated to visceral pleural invasion in early-stage non-small cell lung cancer less than 3 cm

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Background: Visceral pleural invasion (VPI) in early-stage non-small cell lung cancer (NSCLC) is traditionally believed as the result of too much close distance between cancerous lesion and the visceral pleura, but whether there are any other biologic factors correlated to VPI beyond our instinctive thoughts remains unclear. Therefore, we conducted this study to investigate potential factors correlated to VPI comprehensively.

Methods: Both clinical and pathological characteristics of patients undergoing surgery for NSCLC with a size of ≤3 cm were retrospectively analysed.

Results: A total of 403 patients were included for analysis. Patients with VPI had older age than those without (61.1 *vs.* 56.1 years; P<0.001). The mean size of NSCLCs with VPI was larger than those without (2.1 *vs.* 1.6 cm; P<0.001). Moreover, NSCLCs with VPI were located closer to visceral pleura (0.8 *vs.* 1.3 cm; P<0.001) and showed larger rates of pleural indentation (86.8% *vs.* 45.6%; P<0.001) and spiculation (59.7% *vs.* 34.7%; P<0.001) than those without. Pathologically, NSCLCs with VPI tended more likely to be adenocarcinomas (96.9% *vs.* 92.7%; P=0.097), and was more likely to be poorly differentiated (38.0% *vs.* 15.3%; P<0.001), to have cancer embolus (6.2% *vs.* 0.7%; P=0.001) and lymph node metastasis (29.5% *vs.* 10.2%; P<0.001) than those without. Besides shorter distance to visceral pleura [odds ratio (OR)=2.169, 95% CI: 1.221–3.855; P=0.008], older age [OR =2.119, 95% confidence interval (CI): 1.255–3.503; P=0.005], pleural indentation (OR =3.679, 95% CI: 1.888–7.169; P<0.001), adenocarcinoma (OR =4.741, 95% CI: 1.383–16.255; P=0.013), and poor tumor differentiation (OR =11.816, 95% CI: 4.470–31.234; P<0.001) were also found to be closely correlated to VPI in early-stage NSCLC.

Conclusions: Besides shorter distance to visceral pleura and pleural indentation, elderly, adenocarcinoma, and poor tumor differentiation were novel biologic factors correlated to VPI in early-stage NSCLC, which may explain why VPI was an unfavorable prognostic factor for early-stage NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); early stage; pleural invasion; correlated factors

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Introduction

Lung cancer is the leading cause of cancer related death worldwide (1,2), and non-small cell lung cancer (NSCLC) is reported to account for about 85% of all lung cancers. With the advancement of medical screening methods, more and more cases of early-stage NSCLC are being discovered (3). As for the prognosis of early-stage NSCLC, besides tumor size and lymph node metastasis, pleural invasion

is also found to be a significant prognostic factor (4,5). Previous studies have shown that patients with visceral pleural invasion (VPI) yield significantly worse survival than patients without (5,6). In the 8th edition of the TNM classification for NSCLC, if a tumor shows VPI, it increases the T descriptor from T1 to T2 and upstages a tumor from stage IA to stage IB, even when the tumor is less than 3 cm in size (7). Traditionally, the underline mechanism of VPI is instinctively believed to be the result of too much close distance between cancerous lesion and the visceral pleura. However, this explanation cannot fully answer the question why the postoperative prognosis of NSCLCs less than 3 cm with positive VPI is still worse than that of those without, considering the fact that the physical factor of distance had already disappeared after the tumor was completely resected. Therefore, there must be some uncovered biologic factors, beyond that physical factor, affecting long-term prognosis. As a result, it is of great importance to investigate further on the clinicopathological characteristics of VPI and factors correlated to VPI in NSCLC, especially in early-stage NSCLC (diameter ≤3 cm) comprehensively. Previously, only a scarce of studies have explored the correlated factors of VPI in NSCLC and controversial conclusions have been made among these studies (8-10). Moreover, most of these studies mainly focused on computed tomography (CT) characteristics without analysing the impact of pathological features on VPI (8-10). Therefore, in this study, we tried to investigate comprehensively on the factors correlated closely to VPI in early-stage NSCLC by analysing both clinical and pathological characteristics. To our knowledge, our study is the most comprehensive analysis of correlated factors of VPI in early-stage NSCLC with the largest sample size.

Methods

Patients

We retrospectively collected the clinicopathological data of patients who underwent lobectomy or segmentectomy with systematic lymph node dissection or lymph node sampling for NSCLC at our department between January 2015 to December 2016. Contrast-enhanced chest CT, brain magnetic resonance imaging or CT, upper abdominal CT, bone scanning, and cardiopulmonary tests were routinely performed in all patients before surgery. Inclusion criteria included: (I) cancer nodule ≤3 cm in diameter measured on chest CT scans without nodal and distant metastases; (II) patients received lobectomy or segmentectomy with systematic lymph node dissection or lymph node sampling. The following patients were excluded from the study: (I) patients who had received chemotherapy, radiotherapy and/or chemoradiotherapy preoperatively; (II) patients with synchronous multiple primary lung cancers or secondary pulmonary cancers. Since our study was a retrospective study and analyzed anonymously, the committee waived the need for consent.

Preoperative clinical data on age, gender, tumor history, tumor location, tumor size and distance to visceral pleura as well as tumor features including pleural indentation [defined as tumor indentation of the visceral pleura connecting the tumor to the pleura (10,11)] and tumor margin spiculation on CT scans were collected. Postoperative pathological data on tumor type, differentiation, cancer embolus, lymph node involvement and VPI were also well collected. According to the definition of VPI for TNM staging system (4), VPI was categorized into three groups: PL0 as no pleural involvement; PL1 as invasion beyond the elastic layer without being exposed on the pleural surface; PL2 as invasion to the surface of the visceral pleura. PL0 was defined as without VPI, while PL1 and PL2 were both defined as VPI (4). Because we aimed to explore the correlated factors of VPI in early-stage NSCLC, we simply divided those patients into two groups according to status of VPI (VPI negative group and VPI positive group).

Statistical analysis

Data were represented as the mean ± standard deviation (SD) for continuous variables or number and percentage (%) for categorical variables. Student's *t*-test or the Mann-Whitney non-parametric U-test was applied for comparing continuously distributed data between groups, and Chi-squared test or Fisher's exact test was applied to categorical data between groups. Multivariate logistic regression analysis was applied to identify significantly correlated factors for VPI. The statistical analysis was performed using the SPSS 22.0 (IBM, Armonk, NY, USA). A two-sided P value of <0.05 was considered statistically significant.

Results

Baseline characteristics of the included patients with early-stage NSCLC

A total of 403 patients who met the inclusion criteria were

included for analysis. The baseline characteristics of those patients were shown in *Table 1*. The mean age of those patients was 57.7±10.9 years old with a male to female ratio of 1:0.7. Only a small proportion of patients (6.5%) had previous tumor history. Most of those NSCLCs were located in left and right upper lobes. The mean size of those NSCLCs was 1.8 cm, and the mean distance between the cancers to visceral pleura was 1.2 cm. On CT scans, more than half of those NSCLCs (58.8%) showed pleural indentation, and nearly half of those NSCLCs (42.7%) had spiculation. Postoperatively, most of those NSCLCs (94.0%) were found to be adenocarcinomas, and the rest were squamous cell carcinomas (6.0%). About one third of those NSCLCs (32.8%) were found to be well differentiated, and 44.7% of them were moderately differentiated, and the rest (22.6%) were poorly differentiated. Only a small proportion of those NSCLCs (2.5%) were found to have cancer embolus within the cancer tissues. Sixty-six of those NSCLCs (16.4%) were found to have positive lymph node metastasis. As for the status of VPI, 129 patients (32.0%) were found to have VPI, while 274 patients (68.0%) have negative VPI.

Baseline characteristics of patients with positive VPI

A total of 129 patients were found to have positive VPI pathologically. The baseline characteristics of patients with positive VPI were shown in *Table 1*. The mean age of those patients was 61.1±9.0 years old with a male to female ratio of 1:0.8. Only a small proportion of patients (6.5%) had previous tumor history. Most of those NSCLCs with positive VPI were located in left and right upper lobes. The mean size of those NSCLCs with positive VPI was 2.1 cm, and the mean distance of the cancers to visceral pleura was 0.8 cm. On CT scans, most of those NSCLCs with positive VPI (86.8%) showed pleural indentation, and more than half of those NSCLCs with positive VPI (59.7%) had spiculation. Postoperatively, most of those NSCLCs with positive VPI (96.9%) were found to be adenocarcinomas. Only a small proportion of those NSCLCs with positive VPI (6.2%) were found to be well differentiated, and more than half of them (55.8%) were moderately differentiated, and more than one third of them (38.0%) were poorly differentiated. Only a small proportion of those NSCLCs with positive VPI (6.2%) were found to have cancer embolus within the cancer tissues. Thirty-eight of those early-stage NSCLCs with positive VPI (29.5%) were found to have positive lymph node metastasis.

Comparison of characteristics between patients with VPI and patients without

The characteristics of patients with VPI were compared with those without VPI in *Table 1*. Patients with VPI had significantly older age than those without (61.1 *vs.* 56.1 years; P<0.001). When those patients were grouped into two groups by age, the percentage of patients with an age of >60 years in the VPI positive group was significantly higher than that in VPI negative group (57.4% *vs.* 36.9%; P<0.001). There was no significant difference of gender ratio and rate of previous tumor history between those two groups. As for tumor location, VPI was more likely to be involved in NSCLCs located in right upper and middle lobes. The mean size of NSCLCs with VPI was significantly larger than those without (2.1 *vs.* 1.6 cm; P<0.001), and when those patients were grouped into two groups by tumor size, the percentage of patients with a tumor size of >2 cm in the VPI positive group was significantly higher than that in VPI negative group (58.9% *vs.* 29.2%; P<0.001). Moreover, NSCLCs with VPI were located significant closer to visceral pleura than those without (0.8 *vs.* 1.3 cm; P<0.001), and when those patients were grouped into two groups by nodule's distance to the visceral pleura, the percentage of cancerous nodules with an distance of ≤1 cm in the VPI positive group was significantly higher than that in VPI negative group (69.8% and 48.5%; P<0.001). On CT scans, NSCLCs with VPI showed significantly larger rates of pleural indentation (86.8% *vs.* 45.6%; P<0.001) and spiculation (59.7% *vs.* 34.7%; P<0.001) than those without. Postoperatively, NSCLCs with VPI tended more likely to be adenocarcinomas (96.9% *vs.* 92.7%; P=0.097). Notably, NSCLCs with VPI were more likely to be poorly differentiated than those without (the percentage of poorly differentiated NSCLCs: 38.0% *vs.* 15.3%; P<0.001). Moreover, NSCLCs with VPI were significantly more likely to have cancer embolus in the cancer tissues than those without (6.2% *vs.* 0.7%; P=0.001). In addition, NSCLCs with VPI were also significantly more likely to have lymph node metastasis than those without (29.5% *vs.* 10.2%; P<0.001).

Multivariate logistic regression analysis for identifying correlated factors for VPI

In order to identify potential factors closely correlated to VPI in early-stage NSCLC, a multivariate logistic regression analysis was performed (*Table 2*). Age, distance

Table 1 Baseline characteristics of the included patients

Characteristics	Total, n (%)	VPI negative, n (%)	VPI positive, n (%)	P
Number	403	274	129	
Age (years)				0.000
≤60	228 (56.6)	173 (63.1)	55 (42.6)	
>60	175 (43.4)	101 (36.9)	74 (57.4)	
Mean ± SD	57.7±10.9	56.1±11.3	61.1±9.0	0.000*
Gender (male/female)	167/236	111/163	56/73	0.581
Tumor history				0.768
Yes	26 (6.5)	17 (6.2)	9 (7.0)	
No	377 (93.5)	257 (93.8)	120 (93.0)	
Tumor location				0.015
Left upper lobe	117 (29.0)	80 (29.2)	37 (28.7)	
Left lower lobe	55 (13.6)	34 (12.4)	21 (16.3)	
Right upper lobe	142 (35.2)	93 (33.9)	49 (38.0)	
Right middle lobe	28 (6.9)	15 (5.5)	13 (10.1)	
Right lower lobe	61 (15.1)	52 (19.0)	9 (7.0)	
Tumor size (cm)				0.000
≤2	247 (61.3)	194 (70.8)	53 (41.1)	
>2	156 (38.7)	80 (29.2)	76 (58.9)	
Mean ± SD	1.8±0.7	1.6±0.6	2.1±0.6	0.000*
Distance to visceral pleura (cm)				0.000
≤1	233 (57.8)	133 (48.5)	90 (69.8)	
>1	180 (42.2)	141 (51.5)	39 (30.2)	
Mean ± SD	1.2±1.1	1.3±1.1	0.8±0.9	0.000*
Pleural indentation				0.000
Yes	237 (58.8)	125 (45.6)	112 (86.8)	
No	166 (41.2)	149 (54.4)	17 (13.2)	
Spiculation				0.000
Yes	172 (42.7)	95 (34.7)	77 (59.7)	
No	231 (57.3)	179 (65.3)	52 (40.3)	
Pathological type				0.097
Adenocarcinoma	379 (94.0)	254 (92.7)	125 (96.9)	
Squamous cell carcinoma	24 (6.0)	20 (7.3)	4 (3.1)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total, n (%)	VPI negative, n (%)	VPI positive, n (%)	P
Differentiation				0.000
Poor	91 (22.6)	42 (15.3)	49 (38.0)	
Moderate	180 (44.7)	108 (39.4)	72 (55.8)	
well	132 (32.8)	124 (45.3)	8 (6.2)	
Cancer embolus				0.001
Yes	10 (2.5)	2 (0.7)	8 (6.2)	
No	393 (97.5)	272 (99.3)	121 (93.8)	
Lymph node metastasis				0.000
Yes	66 (16.4)	28 (10.2)	38 (29.5)	
No	337 (83.6)	246 (89.8)	91 (70.5)	

*, Mann-Whitney non-parametric U-test. VPI, visceral pleural invasion; SD, standard deviation.

to visceral pleura, pleural indentation, pathological type, and tumor differentiation were found to be significantly correlated to VPI in early-stage NSCLC. Patients with older age [odds ratio (OR) =2.119, 95% CI: 1.255–3.503; P=0.005], shorter distance to visceral pleura (OR =2.169, 95% CI: 1.221–3.855; P=0.008), pleural indentation (OR =3.679, 95% CI: 1.888–7.169; P<0.001), adenocarcinoma (OR =4.741, 95% CI: 1.383–16.255; P=0.013), and poor tumor differentiation (OR =11.816, 95% CI: 4.470–31.234; P<0.001) were more likely to have VPI.

Discussion

Pleural invasion remains to be an important prognostic factor of NSCLC, especially in early-stage NSCLC (5,12). The 5-year survival rates of NSCLC patients were reported to decrease from 75.9–80% (for patients without VPI) to 54.1–63.6% (for patients with VPI) (13,14). Instinctively, the underline mechanism of VPI is believed to be the result of too much close distance between cancerous lesion and the visceral pleura. However, this explanation cannot fully answer the question why the postoperative prognosis in NSCLCs ≤3 cm is still worse in patients with VPI than in those without, considering that the physical factor of distance had already disappeared after the tumor was completely resected. There must be some uncovered biologic factors, beyond physical factor, affecting long-term prognosis. Previous studies mainly focused on exploring how to predict VPI using preoperative clinical factors (8-10), while this study focused on exploring the biological factors correlated to VPI, which might give us a comprehensive understanding of VPI. Therefore, in our current study, in order to explain why patients with positive VPI had a poor prognosis from clinical point of view, we investigated comprehensively on the correlated factors of VPI in early-stage NSCLC by combining both clinical and pathological characteristics. In this study, a total of 403 NSCLC patients with a tumor size ≤3 cm were included for analysis, in which there were 129 patients with positive VPI. On multivariate logistic regression analysis, besides shorter distance to visceral pleura, pleural indentation, elderly, adenocarcinoma, and poor tumor differentiation were also found to have significant impact on the status of VPI in early-stage NSCLC. Therefore, elderly, pathological type of adenocarcinoma, and poor tumor differentiation were fund to be novel biologic correlated factors of VPI in early-stage NSCLC.

VPI has been regarded as an independent indicator of lung cancer invasiveness and aggressiveness (10,15). In pathology, we found that NSCLCs with VPI were more likely to be poor differentiated than those without (P<0.001). Previous study has also observed similar results that there were significantly more tumors with VPI in patients with a tumor of moderate or poor differentiation (P<0.001) (15). Zhang *et al.* (16) found that more lung cancers with VPI tended to be poorly differentiated compared to those without (30.1% *vs.* 25.9%; P=0.159). Moreover, we found that poor tumor differentiation was

Table 2 Multivariate analysis of potential correlated factors of visceral pleural invasion in early-stage lung cancer

Characteristics	OR	95% CI	P
Age (years)			
≤60	Ref	–	–
>60	2.119	1.255–3.503	0.005
Gender			
Male	0.874	0.505–1.513	0.631
Female	Ref	–	–
Tumor history			
Yes	0.617	0.212–1.797	0.376
No	Ref	–	–
Tumor size (cm)			
≤2	Ref	–	–
>2	1.461	0.844–2.532	0.176
Distance to visceral pleura (cm)			
≤1	2.169	1.221–3.855	0.008
>1	Ref	–	–
Pleural indentation			
Yes	3.679	1.888–7.169	0.000
No	Ref	–	–
Spiculation			
Yes	1.201	0.696–2.072	0.511
No	Ref	–	–
Pathological type			
Adenocarcinoma	4.741	1.383–16.255	0.013
Squamous cell carcinoma	Ref	–	–
Differentiation			
Poor	11.816	4.470–31.234	0.000
Moderate	7.089	3.048–16.489	0.000
Well	Ref	–	–
Cancer embolus			
Yes	2.440	0.405–14.693	0.330
No	Ref	–	–
Lymph node metastasis			
Yes	1.735	0.859–3.503	0.124
No	Ref	–	–

Ref, reference; OR, odds ratio.

also significantly correlated to VPI in early-stage lung cancer (poor differentiation: OR =11.816, 95% CI: 4.470–31.234; P<0.001; moderate differentiation: OR =7.089, 95% CI: 3.048–16.489; P<0.001) in the multivariate analysis. Because tumors with poor differentiation were significantly correlated with overexpression of unfavorable prognostic biomarkers such as Vimentin (17) and RBX1 (18), showing more aggressive and invasive biologic behavior than those well-differentiated tumors. Therefore, VPI may be similarly correlated to those unfavorable biomarkers, which may explain why patients with VPI had worse prognosis than those without. Notably, in our study, we found that the percentage of adenocarcinoma in VPI positive group tended to be higher than that in VPI negative group (96.9% *vs.* 92.7%; P=0.097) and in the multivariate analysis, we found that pathological type was significantly correlated to VPI in early-stage NSCLC. Previously, Lakha *et al.* have also found that compared to patients without VPI, patients with VPI were more likely to present with adenocarcinoma (P<0.001) (6). However, most of previous studies did not found pathological type to be a significantly correlated factor of VPI in lung cancer (8-10), which we believe was due to very limited cases of squamous cell carcinoma available for analysis. Previous experimental study has shown that lung adenocarcinoma was more aggressive and invasive than squamous cell carcinoma with a poorer prognosis (19). Therefore, our finding that adenocarcinoma is significantly correlated to VPI added to the evidence pool that adenocarcinoma has more aggressive and invasive biologic behavior from clinical analysis. Moreover, in our study, similar to previous studies (10,15,16), we found that NSCLCs with VPI were more likely to have lymph node metastasis than those without (29.5% *vs.* 10.2%; P<0.001), which added to the evidence that VPI served as an indicator of lung cancer invasiveness and aggressiveness thus leading to a poor prognosis. Taken together, VPI was related to poor tumor differentiation, adenocarcinoma, and lymph node metastasis, which may help explain why VPI was a significant unfavorable prognostic factor of early-stage NSCLC patients. Therefore, our results might justify providing adjuvant therapy for patients with VPI-positive early-stage NSCLC.

Interestingly, in our study, patients with VPI showed significantly older mean age than patients without (61.1 *vs.* 56.1 years; P<0.001). Similar result has also been observed by Lakha *et al.* (6), and they found that the percentage of patients more than 60 years old in VPI positive group was significantly higher than that in VPI negative group

(P=0.02). Moreover, Ebara *et al.* found that patients with VPI tended to be older than patients without (68.5 *vs.* 65.9 years; P=0.061) (8). However, other studies did not find any difference of age between patients with VPI and those without (9,10,15,16,20,21). But surprisingly, in our study, older age was found to be a significantly correlated factor of VPI in early-stage NSCLC (OR =2.119, 95% CI: 1.255–3.503; P=0.005) in the multivariate analysis. However, previous evidence has shown that lung cancers in aged individuals have a less invasive behavior than those in younger ones (22). One possible reason for our result that older age was significantly correlated to VPI in early-stage NSCLC is that in China, older patients have less utilization of screening than the younger ones and often ignore slight symptoms due to the fact that they have retired. Therefore, older patients are less likely to be referred to clinic, which leads to a more advanced stage in older patients.

NSCLCs with VPI showed larger tumor size than those without (2.1 *vs.* 1.6cm; P<0.001) in our study. Previously, Ebara *et al.* (8) have also found that the mean tumor size of lung cancer with VPI was significantly larger than that of those without VPI in early-stage lung cancer (1.67 *vs.* 1.43 cm; P=0.001). Several other studies have also showed that VPI was found more in lung cancers with larger tumor size (6,10,16). However, Qi *et al.* (9), Nitadori *et al.* (20) and Hsu *et al.* (21) did not found any difference of size between lung cancers with VPI and those without. In the multivariate logistic regression analysis, tumor size was not found to be significantly correlated to VPI in our study, which agreed with most of previous studies (8,9). It is believed that tumor size does have certain impact on its invasive behavior, but in our study, all those NSCLCs had a tumor size less than 3 cm. Therefore, for those early-stage NSCLCs (cT1), tumor size may show less impact on VPI than other factors. Traditionally, VPI in lung cancer is believed to be the result of too much close distance between cancerous lesion and the visceral pleura. In our study, NSCLCs with VPI were located closer to the visceral pleura than those without (mean distance: 0.8 *vs.* 1.3 cm; P<0.001). Previously, Ebara *et al.* (8) have also shown that distance to visceral pleura was shorter in lung cancers with VPI than those without (mean distance: 1.2 *vs.* 1.5 cm; P=0.003). Moreover, Qi *et al.* (9) have also found that more lung cancers with VPI were located within 5mm to visceral pleura (P<0.001). Besides Qi *et al.*'s study (9), our study also proved that shorter distance to visceral pleura (OR =2.169, 95% CI: 1.221–3.855; P=0.008) was significantly correlated to VPI in early-stage NSCLC in the multivariate analysis. It is reasonable that the closer a tumor is located to the visceral pleura, the more likely it is to have VPI. On CT scan, NSCLCs with VPI were more likely to have pleural indentation than those without and pleural indentation was found to be significantly correlated to VPI in early-stage NSCLC (OR =3.679, 95% CI: 1.888–7.169; P<0.001) in the multivariate analysis. Previous studies have also proved that pleural indentation was an independent predictive factor of VPI in lung cancer (9,10). Because pleural indentation may suggest the existence of a tumor infiltrating the pleural or pleural dissemination, it serves as a sign suggestive of pulmonary malignancy and possible diagnosis of VPI (9,10,21). Therefore, our study added to the evidence that pleural indentation was a significantly correlated factor of VPI in early-stage NSCLC.

Our study has several limitations. First, our study is a retrospective study, which could limit our analytical validity. Second, in this study, we only grouped patients into VPI positive group and VPI negative group and did not analyse the correlated factors of PL1 and PL2 groups respectively. Finally, even though our study has the largest sample size compared to previous studies, more similar studies and multicenter researches are needed to update and confirm our current conclusions.

Conclusions

In this study, we found that age, distance to visceral pleura, pleural indentation, pathological type, and tumor differentiation had significantly impacts on the status of VPI in early-stage NSCLC. Therefore, besides shorter distance to visceral pleura and pleural indentation, elderly, adenocarcinoma, and poor differentiation were novel biologic factors significantly correlated to VPI in early-stage NSCLC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the Ethics

Committee of West China Hospital (No. 20171217).

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