Smoking and Timing of Cessation*

Impact on Pulmonary Complications After Thoracotomy

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Study objective: **The benefit of smoking cessation just prior to surgery in preventing postoperative pulmonary complications has not been proven. Some studies actually show a paradoxical increase in complications in those quitting smoking only a few weeks or days prior to surgery. We studied the effect of smoking and the timing of smoking cessation on postoperative pulmonary complications in patients undergoing thoracotomy.**

Design and setting: **Prospective study conducted in a tertiary care cancer center in 300 consecutive patients with primary lung cancer or metastatic cancer to the lung who were undergoing anatomical lung resection.**

Results: **The groups studied were nonsmokers (21%), past quitters of > 2 months duration (62%), recent quitters of < 2 months duration (13%), and ongoing smokers (4%). Overall pulmonary complications occurred in 8%, 19%, 23%, and 23% of these groups, respectively, with a significant difference between nonsmokers and all smokers ($p = 0.03$) but no difference among the subgroups of smokers ($p = 0.76$). The risk of pneumonia was significantly lower in nonsmokers (3%) compared to all smokers (average, 11%; $p < 0.05$), with no difference detected among subgroups of smokers ($p = 0.17$). Comparing recent quitters and ongoing smokers, no differences in pulmonary complications or pneumonia were found ($p = 0.67$). Independent risk factors for pulmonary complications were a lower diffusing capacity of the lung for carbon monoxide (DLCO) [odds ratio [OR] per 10% decrement, 1.41; 95% confidence interval [CI], 1.17 to 1.70; $p = 0.01$) and primary lung cancer rather than metastatic disease (OR, 3.94; 95% CI, 1.34 to 11.59; $p = 0.003$). Among smokers, a lower DLCO percent predicted (OR per 10% decrement, 1.42; 95% CI, 1.16 to 1.75; $p = 0.008$) and a smoking history of > 60 pack-years (OR, 2.54; 95% CI, 1.28 to 5.04; $p = 0.0008$) were independently associated with overall pulmonary complications.**

Conclusions: **In patients undergoing thoracotomy for primary or secondary lung tumors, there is no evidence of a paradoxical increase in pulmonary complications among those who quit smoking within 2 months of undergoing surgery. Smoking cessation can safely be encouraged prior to surgery** ***(CHEST 2005; 127:1977–1983)***

Key words: lung cancer; postoperative care; pulmonary complications; smoking; thoracic surgery; tobacco cessation

Abbreviations: CI = confidence interval; DLCO = diffusing capacity of the lung for carbon monoxide; OR = odds ratio

Smoking has been found to be a risk factor for the development of postoperative complications after many types of surgery, even in the absence of underlying chronic lung disease. The relative risk of complications after surgery for smokers compared to nonsmokers has been reported to increase from 1.4-fold to 4.3-fold.[1–4] Smoking cessation prior to surgery is widely encouraged, but the value of stopping only a few days to weeks prior to an operation is not known. A decrease in postoperative pulmonary complications due to smoking cessation is thought to be related to physiologic improvement in ciliary action, macrophage activity, and small airways function, as well as a decrease in sputum production. These changes can take weeks to months to occur.[5,6]

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Some studies[7,8] have suggested that stopping smoking only a few weeks prior to surgery may lead to an unexpected or paradoxical increase in the rate of pulmonary complications, and recommendations have been made that surgery should be delayed for 8 weeks after smoking cessation.

The effect of smoking and the time of smoking cessation on postoperative pulmonary complications in patients undergoing thoracotomy for primary or secondary lung tumors is unclear. Many of these patients, particularly those with primary lung cancer, are current or past smokers, and some have COPD. Since the extent of lung resection may affect outcome, lung-sparing surgery, such as wedge resection, is often preferentially performed in those with marginal pulmonary reserve, making risk prediction difficult. Only one retrospective study[9] has looked at patients undergoing thoracotomy for lung cancer and found that it took 5 weeks of smoking abstinence for complications in smokers to decrease to the level of ex-smokers. The complication rate was highest in those who quit smoking within 4 weeks of surgery. Since patients who are potentially capable of undergoing resection proceed to surgery as quickly as is feasible, the impact of quitting the smoking of cigarettes in the preoperative period on postoperative complications is an important issue. We undertook this prospective study to clarify the relationship of postoperative pulmonary complications to smoking history and the timing of smoking cessation in those scheduled to undergo the anatomical resection of primary or secondary lung tumors.

Materials and Methods

Consecutive thoracic surgical patients who were > 18 years old, and were scheduled to undergo thoracotomy for the treatment of primary or secondary lung tumors at Memorial Sloan-Kettering Cancer Center between September 1999 to November 2001, were prospectively recruited. The protocol was approved by the institutional review board, and patients gave written consent. Patients were excluded from the study for undergoing a second surgery during the same hospital admission, or for undergoing concomitant rib, chest wall, diaphragmatic, pericardial, or pleural resections. Smoking status (*ie*, number of years smoked, packs per day, timing of smoking cessation, and nicotine replacement therapy) was determined by a questionnaire that was administered at the time of surgery by a research assistant. Patients were assured that answers would not be communicated to the care team. The groups studied were as follows: nonsmokers; past quitters, who stopped smoking > 2 months before surgery; recent quitters, who stopped smoking > 1 week and ≤ 2 months before surgery; and ongoing smokers, who smoked to within the week of undergoing surgery or did not stop smoking. Patients received standard general anesthesia and postoperative analgesia, which was surgeon-specific, and consisted of IV morphine patient-controlled analgesia ($n = 93$) or epidural fentanyl patient-controlled analgesia ($n = 207$).

The following postoperative pulmonary complications were considered as study end points and were recorded throughout the hospital stay: respiratory failure requiring ICU admission and/or intubation; pneumonia (new pulmonary infiltrate with fever treated with IV antibiotics); atelectasis requiring bronchoscopy (need determined by the surgical team); pulmonary embolism (diagnosed by CT scan and treated); and the need for supplemental oxygen at hospital discharge. No patient had required the use of oxygen prior to undergoing surgery. Transient hypoxemia and bronchospasm were not study end points. Once discharged from the hospital, an investigator or research nurse monitored patients for complications for 30 days from the time of surgery and queried patients about intercurrent hospitalizations or emergency department visits.

Statistical Analysis

We anticipated that the ratio of subjects with complications to subjects without complications in the study population would be 1:4. The required sample size for detecting a difference of 0.125 with 0.80 power between smokers and nonsmokers was 300 patients. The distribution of clinical characteristics, smoking history, pulmonary complications, and length of stay in categories of smoking cessation were compared using the χ^2 test, Fisher exact test, t test, or analysis of variance, as appropriate. The overall pulmonary complication and pneumonia rates were compared between nonsmokers and all smokers, and also among the categories of smokers. Continuous variables are presented as the mean $\pm$ SD and median (range), as some distributions were skewed. Multivariate analysis of the joint effects of prognostic factors was studied using stepwise logistic regression. All variables whose univariate tests resulted in a p value of < 0.2 were considered in the multivariate analysis model. Box-Cox transformations were applied to pack-years of cigarette smoking and length of hospital stay to reduce skewness. Imputation was employed for a small number of missing values. Two missing values of packs of cigarettes smoked per day were imputed by gender-adjusted median values to compute the total number of pack-years. Six missing percent predicted values for diffusing capacity of the lung for carbon monoxide (DLCO) were imputed from a linear regression on FEV_1 percent predicted values. Fourteen missing DLCO and FEV_1 percent predicted values were excluded from multivariant prognostic factor analysis for pulmonary complications. All test results with a p value of < 0.05 were considered to indicate statistical significance. A statistical software package (SAS, release 9.0; SAS Institute; Cary, NC) was used for all analyses.

Results

Patient demographic and clinical characteristics are shown in Table 1. A total of 300 consecutive cancer patients who underwent thoracotomy for anatomical lung resection were studied. The mean age was greater among past quitters when compared to nonsmokers ($p = 0.03$) [Table 1]. Nonsmokers had significantly greater FEV_1 values than past or recent quitters. Similarly, nonsmokers had significantly greater DLCO percent predicted values when compared to past quitters, recent quitters, or ongoing smokers ($p < 0.05$, respectively). In nonsmokers, proportionately more wedge resections and fewer lobectomies were performed in comparison to past or recent quitters ($p = 0.003$ and $p = 0.001$, respec-

Table 1—*Clinical Characteristics by Smoking Group

Characteristics	All (n = 300)	Nonsmokers (n = 64)	Past Quitters (n = 184)	Recent Quitters (n = 39)	Ongoing Smokers (n = 13)	p Value
Age, years						
Mean ± SD	64 ± 12	60 ± 16	66 ± 10	62 ± 9	63 ± 12	0.004†
Median	66	63	68	61	62	
Sex						
Female	156 (52)	38 (59)	88 (48)	25 (64)	5 (39)	0.12
Male	144 (48)	26 (41)	96 (52)	14 (36)	8 (62)	
FEV_1,‡ % predicted						
Mean	84 ± 22	97 ± 22	81 ± 21	80 ± 19	88 ± 23	< 0.0001
Median	85	100	83	81	91	
DLCO,§ % predicted						
Mean	70 ± 20	83 ± 21	67 ± 20	66 ± 16	66 ± 16	< 0.0001
Median	70	86	65	66	63	
Surgical procedure‖						
Lobectomy	212 (71)	31 (48)	135 (73)	36 (92)	10 (77)	0.0001
Wedge resection	73 (24)	29 (45)	38 (21)	3 (8)	3 (23)	
Pneumonectomy	15 (5)	4 (6)	11 (6)	0 (0)	0 (0)	

*Values given as mean ± SD or No. (%), unless otherwise indicated.

†Values represent overall differences among the groups. Used the Welch analysis of variance (for heterogeneity of age variance). Past quitters were significantly older than nonsmokers and recent quitters (p = 0.03, respectively, after Bonferroni adjustment).

‡Nonsmokers had significantly greater FEV_1 percent predicted values than past or recent quitters ($p < 0.05$, respectively, using the *post hoc* Duncan multiple comparison procedure).

§Nonsmokers had significant greater DLCO percent predicted values than past quitters, recent quitters, and ongoing smokers ($p < 0.05$, respectively, using the *post hoc* Duncan multiple comparison procedure).

‖Past and recent quitters underwent a significantly higher proportion of lobectomies than nonsmokers (p = 0.003 and p = 0.001, respectively, after Bonferroni adjustment). Recent quitters underwent lobectomy significantly more often than past smokers before Bonferroni adjustment (p = 0.04) but this was not significant after the adjustment.

tively) [Table 1]. This is likely because wedge resection is preferred for the resection of metastatic disease and smokers would be more likely to have primary lung cancer rather than metastasis. Of the 300 patients, 221 patients had resectable lung cancer (53% women and 47% men) with 199 patients (90%) being smokers or ex-smokers. Cigarette consumption in smokers with primary lung cancer was substantial, with a mean consumption history of 56 ± 31 pack-years. There was a marginal trend toward lower cigarette consumption in women vs men (52 ± 29 vs 59 ± 32 pack-years, respectively; p = 0.09). The median consumption history in women was 50 pack-years, and in men it was 58 pack-years. The great majority of patients (69%) had quit smoking before the diagnosis of lung cancer was made, with the mean time since smoking cessation being 11.3 years (median, 10 years).

The characteristics of the 51 of 300 patients (17%) in whom pulmonary complications developed are shown in Table 2. Univariate risk factors associated with pulmonary complications were a history of smoking, preoperative chemotherapy, lower FEV_1 or DLCO percent predicted, and the diagnosis of primary lung cancer. On multivariate analysis, a lower DLCO percent predicted (odds ratio [OR] per 10% decrement, 1.41; 95% confidence interval [CI], 1.17 to 1.70; p = 0.0003) and the diagnosis of primary lung cancer (OR, 3.94; 95% CI, 1.34 to 11.59; p = 0.003) were independently associated with the occurrence of pulmonary complications (Table 2). A separate analysis was performed for overall complication excluding pulmonary embolism. In multivariate logistic regression, DLCO percent predicted remained a strong predictor (p = 0.0001). Tumor presentation (primary vs secondary) remained significant (p = 0.02) when adjusted for DLCO percent predicted. Meanwhile, chemotherapy (yes vs no) became a significant predictor (p = 0.01) when adjusted for DLCO percent predicted and was interchangeable with tumor presentation in the final model. Length of hospital stay was significantly greater in patients in whom pulmonary complications developed compared to those in whom they did not develop (median, 8 vs 6 d; $p < 0.0001$).

The distribution of pulmonary complications according to smoking status is shown in Table 3. The overall pulmonary complication rate (nonsmokers, 8%; past quitters, 19%; recent quitters, 23%; ongoing smokers, 23%; smokers overall, 19%) differed significantly between nonsmokers and all smokers (p = 0.03) but did not differ among the categories of smokers (p = 0.76). A similar result was observed when pulmonary embolism was excluded from the overall pulmonary complication (rates were 6%, 17%, 21%, and 23% in the four groups, respectively). Pneumonia was significantly dif-

Table 2—*Clinical Characteristics by Postoperative Pulmonary Complications

Variable	Complications				p Value (Univariate Analysis)	p Value (Multivariate Analysis)	OR (95% CI)
	No (n = 249)		Yes (n = 51)				
Age	64	12	66	11	0.34		
Sex							
Female	130	83	26	17	0.87		
Male	119	83	25	17			
Ever smoked							
No	59	92	5	8	0.03		
Yes	190	81	46	20			
Chemotherapy							
No	215	85	38	15	0.03		
Yes	34	72	13	28			
FEV_1, % predicted	86	22	78	21	0.02		
DLCO, % predicted	73	20	61	17	< 0.0001	0.0003	1.41 (1.17–1.70)†
Surgical procedure							
Wedge resection	62	85	11	15	0.79		
Lobectomy	174	83	38	18			
Pneumonectomy	13	87	2	13			
Tumor presentation							
Secondary	74	94	5	6			
Primary	175	79	46	21	0.003	0.01	3.94 (1.34–11.59)
Length of stay,‡ d	7	4	10	6	< 0.0001		
Median (range)	6	(2–23)	8	(3–30)			

*Values given as the mean ± SD or No. (%), unless otherwise indicated.
†Per 10% decrease in D^{LCO} percent predicted.
‡Analysis was based on Box-Cox transformed data.

ferent between nonsmokers and all smokers (3%, 10%, 15%, and 23%, respectively, with an average of 11% in all smokers; $p < 0.05$) [Table 3]. There was no significant difference in pneumonia rate among the smoking groups ($p = 0.17$). There was no difference in overall pulmonary complication or pneumonia rate ($p = 0.67$) when comparing recent quitters and ongoing smokers. The incidence of pneumonia was 8% (17 of 207 patients) in patients who had received epidural analgesia compared to 14% (13 of 93 patients) in patients who had received IV morphine analgesia ($p = 0.18$). The average length of hospital stay was greater for ongoing smokers compared to nonsmokers ($p < 0.05$) [Table 3]. There were three deaths in men who were aged 62, 72, and 82 years, respectively. All had been smokers, with two being past quitters and one a recent quitter. All had pulmonary complications, and two also had acute coronary syndromes (myocardial ischemia in one patient and myocardial infarction in another).

A separate analysis was performed among smokers

Table 3—*Pulmonary Complications by Smoking Status

Pulmonary Complications	All (n = 300)		Nonsmokers (n = 64)		Past Quitters (n = 184)		Recent Quitters (n = 39)		Ongoing Smokers (n = 13)		p Value*
	No.	%	No.	%	No.	%	No.	%	No.	%	
Overall	51	17	5	8	34	19	9	23	3	23	0.14
Pneumonia	29	10	2	3	18	10	6	15	3	23	0.04†
O_2 at hospital discharge	19	6	2	3	13	7	4	10	0	0	0.44
Atelectasis	11	4	0	0	10	5	1	3	0	0	0.22
Pulmonary embolism	5	2	1	2	3	2	1	3	0	0	0.53
Respiratory failure	3	1	0	0	2	1	1	3	0	0	0.84
Length of stay, d											< 0.05‡
Mean (SD)	7 (4)		6 (4)		8 (4)		8 (6)		9 (5)		
Median	6		5		6		6		7		

*Values represent overall differences among the groups.
†Ongoing smokers and recent quitters had higher incidences of pneumonia than nonsmokers ($p = 0.05$ and $p = 0.03$, respectively, without multiple testing adjustment). After Bonferroni correction, these differences were no longer significant.
‡Ongoing smokers stayed significantly longer at the hospital than nonsmokers ($p < 0.05$, following Box-Cox transformation).

(227 of 300 patients) to evaluate risk factors associated with the development of any pulmonary complication (Table 4) and pneumonia specifically (Table 5). On both univariate and multivariate analyses, risk factors associated with pulmonary complications were smoking > 60 pack-years (OR, 2.54; 95% CI, 1.28 to 5.04; p = 0.0008) and lower DLCO percent predicted (OR per 10% decrement, 1.42; 95% CI, 1.16 to 1.75; p = 0.008). The cutoff value of 60 pack-years was chosen as the 67th percentile of pack-years in both male and female smokers. In univariate analysis, there was a significant association of pneumonia with > 60 pack-years of smoking, lower DLCO percent predicted, and type of surgical procedure (Table 5). In stepwise multivariate logistic regression analysis, smoking history of > 60 pack-years (OR, 3.10; 95% CI, 1.35 to 6.94; p = 0.007) was the only independent risk factor that was associated with postoperative pneumonia. When repeating the same analysis without pulmonary embolism, the results remained similar.

Discussion

In contrast to previous reports,[7,8] this prospective study showed that there was no paradoxical increase in pulmonary complications associated with stopping smoking in the 8 weeks prior to thoracic surgery in comparison to patients with continued smoking until the time of surgery. The incidence of pneumonia in nonsmokers (3%) was significantly lower than that in recent quitters (15%) or ongoing smokers (23%), but was no different than that of past quitters (10%). Independent risk factors for developing any pulmonary complication were a lower DLCO percent predicted and having primary lung cancer. Among smokers, predictive factors for the development of pulmonary complications were a lower DLCO percent predicted and a smoking history of > 60 pack-years. Those who had smoked > 60 pack-years had double the risk of any pulmonary complication developing and triple the risk of pneumonia compared to those who smoked ≤ 60 pack-years. Our study is in agreement with prior work[10–18] confirming that abnormal pulmonary function test results are consistently predictive of postoperative pulmonary complications in those patients undergoing thoracotomy. Smoking status, independent of its relationship to lung function, has been identified as a risk factor for pulmonary complications in some but not all studies.[1,16,17]

Only one prior study[9] has looked at the impact of the timing of smoking cessation on postoperative

Table 4—*Pulmonary Complications in Smokers

	Pulmonary Complication			Multivariate Analysis	
Variables	No (n = 181)	Yes (n = 46)	p Value (Univariate Analysis)	OR (95% CI)	p Value
Age, yr	65 ± 10	67 ± 10	0.46		
Gender					
Female	87 (79)	23 (21)	0.81		
Male	94 (80)	23 (20)			
Smoking status					
Ongoing smokers	9 (75)	3 (25)	0.80		
Recent quitters	30 (77)	9 (23)			
Past quitters	142 (81)	34 (19)			
Pack-years					
≤ 60	131 (85)	23 (15)	0.004	1.00	
> 60	50 (69)	23 (32)		2.54 (1.28–5.04)	0.0008
FEV_1, % predicted	82 ± 20	77 ± 21	0.11		
DLCO, % predicted	70 ± 19	59 ± 17	0.0004	1.42 (1.16–1.75)†	0.008
Tumor presentation					
Primary	152 (78)	43 (22)	0.10		
Secondary	29 (91)	3 (9)			
Prior chemotherapy					
No	150 (82)	34 (19)	0.17		
Yes	31 (72)	12 (28)			
Surgical procedure					
Wedge	30 (77)	9 (23)	0.88		
Lobectomy	142 (80)	35 (20)			
Pneumonectomy	9 (82)	2 (18)			

*Values given as the mean ± SD or No. (%), unless otherwise indicated.
†Values given per 10% decrease in DLCO percent predicted.

Table 5—*Pneumonia in Smokers

Variable	Pneumonia		p Value (Univariate Analysis)	Multivariate Analysis	
	No (n = 200)	Yes (n = 27)		OR (95% CI)	p Value
Age	66 ± 10	65 ± 11	0.61		
Female	96 (87)	14 (13)	0.71		
Male	104 (89)	13 (11)			
Smoking status					
Ongoing smokers	9 (75)	3 (25)	0.17		
Recent quitters	33 (85)	6 (15)			
Past quitters	158 (90)	18 (10)			
Pack-years					
≤ 60	142 (92)	12 (8)	0.006	1.00	
> 60	58 (80)	15 (21)		3.10 (1.35–6.94)	0.007
FEV_1, % predicted	81 ± 20	79 ± 23	0.57		
DLCO, % predicted	68 ± 19	61 ± 17	0.05		
Tumor presentation					
Primary	170 (87)	25 (13)	0.39		
Secondary	30 (94)	2 (6)			
Prior chemotherapy					
No	163 (89)	21 (11)	0.64		
Yes	37 (86)	6 (14)			
Surgical procedure					
Lobectomy	159 (90)	18 (10)	0.23		
Wedge	32 (82)	7 (18)			
Pneumonectomy	9 (82)	2 (18)			

*Values given as the mean ± SD or No. (%), unless otherwise indicated.

complications after thoracic surgery. In this study, ongoing smokers had a 44% rate of pulmonary complications, while recent quitters had a rate of 54%. In those who had stopped smoking cigarettes for at least 5 weeks, complications started to decline to the levels of ex-smokers and never-smokers (35% and 24%, respectively). A major limitation of this study is that data on both the development of postoperative pulmonary complications and the determination of the exact week of smoking cessation prior to surgery were retrospectively gathered from the medical record. The potential for error in determining the date of smoking cessation is significant. Two previous studies[7,8] have addressed the relationship of the timing of smoking cessation to the incidence pulmonary complications in non-pulmonary resection surgery. In 200 patients who were undergoing coronary artery bypass surgery at the Mayo Clinic, those who had quit smoking at least 8 weeks before undergoing surgery had a 15% rate of pulmonary complications compared to 33% in current smokers.[7] Those who had stopped smoking < 8 weeks before undergoing surgery had the highest complication rate of 57%. Preoperative pulmonary function and the number of pack-years of smoking were found to be independently associated with postoperative pulmonary morbidity. A study at the Syracuse Veterans Administration Hospital in those undergoing elective general, orthopedic, urologic, or cardiovascular surgery found a reduction in complications after smoking cessation of several weeks duration.[8] More complications developed in current smokers who reduced cigarette consumption just prior to undergoing surgery compared to those who continued to smoke (OR, 6.7; 95% CI, 2.6 to 17.1); however, no correction was made for underlying lung function. The reason why complications might increase in recent quitters in these studies is not known, but the authors speculated that the abrupt absence of the irritant effect of cigarette smoking during the perioperative period may have augmented the risk of retained secretions and obstructed airways.[7] A reduction in sputum production post-smoking cessation may have taken more time to occur. Nicotine withdrawal may also be a factor. It has also been suggested that those who reduce smoking prior to surgery may be sicker or more impaired patients who are at increased risk of postoperative complications. In our study, the three smoking groups were similar in terms of pulmonary function, and recent quitters were indeed younger than past quitters.

There are several limitations of our study. We relied on a questionnaire for the determination of smoking status and did not obtain chemical confirmation. By use of an interviewer who was not a member of the care team, however, we sought to encourage candid answers. Statistical power in our study is also limited by the small number of ongoing smokers in our highly motivated patient population

in which most patients chose to stop smoking prior to surgery. Last, our results reflect the pulmonary complications that we chose to monitor that may or may not be associated with smoking, such as pulmonary embolism, but were selected because they were reliably detectable and expected to cause significant morbidity, including the requirement of oxygen therapy on discharge from the hospital, which was one of the end points of the study. We also analyzed the results with the exclusion of pulmonary embolism without any significant change in the conclusions of the study. We acknowledge that our definition of pneumonia may be an overestimate as BAL and cultures were not routinely performed. This definition was used by our surgeons in clinical practice. It is possible that other conditions, such as the transient need for oxygen or mild bronchospasm may have a different relationship to smoking cessation but were not considered as important end points in this study.

Our prospective study provides evidence that stopping smoking in the weeks immediately prior to undergoing thoracotomy for the resection of lung cancer does not confer an increased risk of pulmonary complications. Nonsmokers had lower rates of all pulmonary complications and pneumonia than did all smokers. Although the risk of pneumonia increased with more recent smoking, this did not reach statistical significance. The evidence in our study suggests that physicians should encourage patients with cancer who are still smoking to stop smoking prior to undergoing surgical resection.

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