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ORIGINAL RESEARCH

Prophylactic cranial irradiation in non-small cell lung cancer patients: who might be the candidates?

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Objectives: Brain metastases (BMs) often advance the course of non-small cell lung cancer (NSCLC). We performed an observational study in order to investigate the possible correlation of selected clinical and epidemiological factors with BM appearance in patients suffering from different histological subtypes of NSCLC stage I–IV.

Methods: The study included 161 consecutive patients with NSCLC. Analyzed data included patient- and tumor-related characteristics.

Results: Thirty-nine patients (24.2%) presented BMs within 12 (0–36) weeks of diagnosis. BMs decreased the mean overall survival significantly (15.6 versus 50.7 weeks, $P < 0.001$), with hazard ratio (95% confidence interval) 3.60 (2.42–5.35). The age of the patients with BM was significantly lower than that of the patients without BM (60.8 ± 8.9 versus 66.5 ± 8.5, $P < 0.001$). Patients with BM had significantly higher pack-years consumption (75.9 ± 23.9 versus 58.9 ± 31.9, $P = 0.003$) and larger tumor size compared with patients without BM (size in mm: 55.1 ± 20.1 versus 45.9 ± 19.3, $P = 0.012$). The presence of BM was also correlated with the absence of lung ($P < 0.001$), bone ($P = 0.005$), and adrenal ($P = 0.046$) metastases.

Conclusion: Younger NSCLC patients with high tobacco consumption, large tumor size, and absence of metastases in other organs (lung, bones, adrenal metastases) are at high risk of BM appearance during the course of NSCLC and are candidates for prophylactic cranial irradiation early in the course of the disease.

Keywords: NSCLC, brain metastases, clinical and epidemiological factors, PCI

Introduction

Lung cancer was the leading cause of death from cancer in Europe in 2006, with 334,800 deaths (19.7% of total).[1] Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, representing more than 80% of lung cancer cases.[2]

Brain metastases (BMs) are a frequent complication of NSCLC, especially in patients with locally advanced disease.[3,4] The addition of chemotherapy to radiation therapy (RT) reduces distant metastases and significantly improves survival.[5,6] However, chemoradiotherapy is shown not to reduce the rate of BM,[5] but to be associated with increased rates of overall brain failure (21%–54%) and an increased incidence of the brain as the first site of relapse (15%–30%).[5–8] These findings emphasize the need for treatment specifically directed at brain micrometastases.

Prophylactic cranial irradiation (PCI) has been demonstrated to reduce the incidence or delay the onset of BM in patients with locally advanced NSCLC, after initial treatment in numerous selected nonrandomized and randomized studies.[3,7,9–16] Nevertheless, during the last decade only few studies assessed the clinical and

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epidemiological factors associated with high risk of BM appearance in NSCLC patients with locally advanced disease at diagnosis.[14,17–20] In these studies, several factors such as duration of survival after diagnosis, performance status, chemotherapy regimens, age at diagnosis, sex, and lung cancer histotype and stage have been associated with the risk of BM development.

The authors of this paper hypothesized that among NSCLC patients of stage I–IV may exist a group of patients at high risk of presenting BM that may be protected using PCI. This group should be identified in order to serve as target for future studies of PCI application in NSCLC.

We performed an observational study in order to investigate the possible correlation of selected clinical and epidemiological factors with BM appearance in patients suffering from different histological subtypes of NSCLC stage I–IV.

Methods

The study's cohort

We recruited 161 consecutive patients with a new diagnosis of NSCLC, between January 2003 and March 2009. Patients' selection criteria were as follows: confirmed diagnosis of NSCLC and appropriate staging. The sixth edition of the tumor–node–metastasis (TNM) classification was used.[21]

All patients were treated with surgery and/or chemotherapy and/or radiotherapy according to the current guidelines.[22,23] They were evaluated every 3–6 months, depending on the curative or palliative nature of the initial treatment.

For each patient, the following variables were recorded at the time of diagnosis: age, sex, tobacco consumption, comorbidities, TNM status at diagnosis, tumor histotype, computed tomography (CT) scan features (central/peripheral location, side, lung lobe, size, cavitation, pleural effusion), and bronchoscopic findings. During the study period, the variables of patients with BM were registered and compared with those of patients without BM. All patients gave their informed consent, and the study was approved by the Ethics Committee of the "Sotiria" Chest Diseases Hospital, Athens.

Statistical analysis

Mean values (and standard deviation [SD]) or median values (and interquartile range [IR]) were used to describe quantitative variables. For the comparison of quantitative variables without normal distribution between two groups, and between three or more different groups, the Mann–Whitney test and Kruskal–Wallis test were used, respectively. To compare normal distributed quantitative variables between two groups and between three or more different groups, Student's *t*-test and analysis of variance test were used, respectively.

To control for type I errors, due to multiple comparisons, Bonferroni correction was used, by which the significance level is defined as $0.05/k$ (k = number of comparisons). Logistic regression analysis (stepwise method) was used in order to find independent factors associated with BM presentation. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed from the results of logistic analysis. Kaplan–Meyer method was used to estimate survival curves. To compare survival curves, log rank tests were used. Statistical significance was set at 0.05, and all *P*-values are two tailed. For the statistical analysis, SPSS Statistics 17.0 (IBM Corporation, Somers, NY) and STATA 9.0 (Stata Corp, College Station, TX) programs were used.

Results

Description of the cohort

Patient's characteristics are summarized in Table 1. Most of the patients were males (88.8%), with mean age (±SD) 65.1 ± 8.9 years and mean tobacco consumption (±SD) of 63.0 ± 31.0 pack-years.

Most of the tumors were located centrally (85.7%). Therefore, they were located within the range of fiber bronchoscopy, which revealed mainly mucosal or submucosal infiltration (67.7%). Most of the tumors were on the right lung (52.2%) and on the upper lobes (70.2%). The mean size (±SD) of the tumors, measured on CT scanners, was 48.1 ± 19.8 mm. Almost one-third (36.6%) were accompanied by pleural effusion at presentation. During the disease course, 37.3% of the patients presented lung, 36.6% bone, 23% liver, and 21.7% adrenal metastases.

BMs

BMs were presented in 24.2% of the patients. The median time (IR) of BM appearance was 12 (0–36) weeks from diagnosis. At the time of BM presentation, most of the patients were classified as T4 (42.9%) and N2 (43.5%) by the TNM classification. A total of 59% of the BMs were ≥2, mostly unilateral (53.8%).

The overall survival of the cohort was influenced by the presence of BM (Figure 1). Survival time of the patients with BM was shorter compared with those without BM: 15.6 weeks (standard error [SE] = 1.9) versus 50.7 weeks (SE = 4.8, $P < 0.001$). The hazard ratio, upon Cox model, for the presence of BM was 3.60 (95% CI 2.42–5.35, $P < 0.001$).

Table 1 Patient- and disease-related characteristics

Characteristic	n (%)
Patient-related variables	
Sex	
Male/female	143 (88.8)/18 (11.2)
Age	
Mean ± SD	65.1 ± 8.9
Pack-years	
Mean ± SD	63.0 ± 31.0
COPD	
No/yes	89 (55.3)/72 (44.7)
Arterial hypertension	
No/yes	98 (60.9)/63 (39.1)
Coronary disease	
No/yes	132 (82.0)/29 (18.0)
Diabetes mellitus	
No/yes	136 (84.5)/25 (15.5)
Gastritis/ulcer	
No/yes	138 (85.7)/23 (14.3)
Hypothyroidism	
No/yes	154 (95.7)/7 (4.3)
Other comorbidity	
No/yes	130 (80.7)/31 (19.3)
Disease-related variables	
Histotype	
Non-differentiated NSCLC	49 (30.4)
Squamous	49 (30.4)
Adenocarcinoma	59 (36.6)
Large cell carcinoma	4 (2.6)
Location	
Central/peripheral	138 (85.7)/23 (14.3)
Bronchoscopic findings	
Mass	36 (22.4)
Infiltration	109 (67.7)
None	16 (9.9)
Lung tumor side	
Right/left	84 (52.2)/77 (47.8)
Lung tumor lobe	
Upper	113 (70.2)
Middle	8 (5.0)
Inferior	40 (24.8)
Lung tumor size	
Mean ± SD	48.1 ± 19.8
Other tumor characteristics	
Pleural effusion	59 (36.6)
Cavitation	12 (7.5)
None	90 (55.9)
T classification (brain metastases)[a]	
T_1/T_2	13 (8.1)/55 (34.2)
T_3/T_4	24 (14.9)/69 (42.9)
N classification (brain metastases)[a]	
N_0/N_1	38 (23.6)/16 (9.9)
N_2/N_3	70 (43.5)/37 (23.0)
Lung metastasis	
No/yes	101 (62.7)/60 (37.3)
Bones metastasis	
No/yes	102 (63.4)/59 (36.6)
Liver metastasis	
No/yes	124 (77.0)/37 (23.0)
Adrenal metastasis	
No/yes	126 (78.3)/35 (21.7)
Other metastasis	
No/yes	144 (89.4)/17 (10.6)
Metastasis brain	
No/yes	122 (75.8)/39 (24.2)
Diagnosis to brain metastases time (weeks)	
Median (IR)	12 (0–36)
Number of brain metastases	
0/1	122 (75.8)/16 (9.9)
2/>2	6 (3.7)/17 (10.6)
Brain metastasis side	
Right	12 (30.8)
Left	9 (23.0)
Bilateral	18 (46.2)
Brain metastasis lobe	
Frontal	9 (23.1)
Parietal	9 (23.1)
Occipital	1 (2.6)
Cerebellum	2 (5.1)
≥2	18 (46.2)

Note: [a]TNM (tumor–node–metastasis) classification.[21]
Abbreviations: COPD, chronic obstructive pulmonary disease; IR, interquartile range; NSCLC, non-small cell lung cancer; SD, standard deviation.

The age of patients with BM was significantly lower compared with that of the patients without BM (60.8 ± 8.9 versus 66.5 ± 8.5, $P < 0.001$) (Table 2). Furthermore, patients with BM had significantly higher pack-years consumption (75.9 ± 23.9 versus 58.9 ± 31.9, $P = 0.003$) and larger tumor size compared with patients without BM (size in mm: 55.1 ± 20.1 versus 45.9 ± 19.3, $P = 0.012$). The presence of BM was also correlated with the absence of lung ($P < 0.001$), bone ($P = 0.005$), and adrenal ($P = 0.046$) metastases.

Patients with right-sided BM presented a significantly lower rate of arterial hypertension (16.7% versus 83.8%, $P = 0.050$) (Table 3). None of the patients with unilobar BM suffered from diabetes, compared with patients with multilobar (≥2 lobes) metastases ($P = 0.015$) (Table 4).

According to regression analysis, age, tobacco consumption in pack-years, and absence of lung or bone metastases represented independent prognostic factors for the appearance of BM (Table 5). In particular, an increase of age reduced the possibility of BM appearance (OR 0.91; 95% CI 0.87–0.96, $P < 0.001$). Conversely, increasing cigarette consumption increased the possibility of BM appearance (OR 1.02; 95% CI 1.001–1.030, $P = 0.006$). Patients without lung

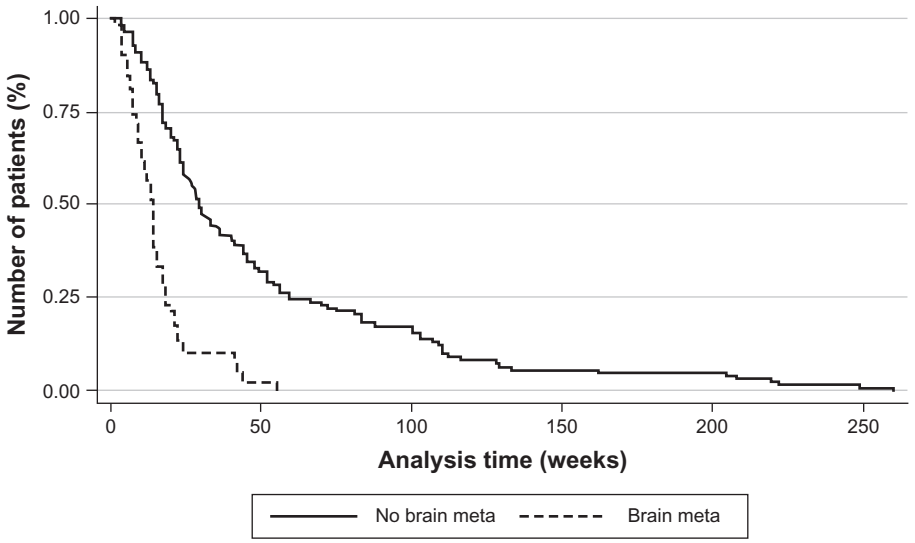

Figure 1 Kaplan–Meier estimation of overall survival (patients with or without brain metastases).
Abbreviation: meta, metastasis.

and bone metastases had 76% and 70% higher possibility of presenting BM, respectively.

Discussion

The main finding of this observational study was that younger NSCLC patients with high tobacco consumption, large tumor size, and absence of other metastases are at high risk of developing BMs during the course of their disease.

BM appearance and survival

Robnett et al reported that the timing of chest irradiation can influence the risk of brain recurrences: the rate of BM is 27% in patients receiving induction chemotherapy before thoracic RT compared with 15% in patients who are treated with concurrent chemoradiation.[17] The 2-year actuarial rate of BM is 39% versus 20%. The authors hypothesize that early aggressive locoregional and systemic treatment could better control regional disease, which in turn affects the development of brain relapses. In accordance with these findings, BMs presented in 39 out of 161 patients (24.2%) in this present study. The rate of BM is quite similar to the rate which has been previously reported by Robnett et al for patients who were not treated with concurrent chemoradiotherapy. The lack of a radiotherapy department in the "Sotiria" Chest Diseases Hospital renders impossible the application of concurrent chemoradiotherapy and therefore leads to the application of the sequential module.

Once diagnosed, BMs are mostly treated with whole-brain radiotherapy, having a response rate of 45%–81% in NSCLC.[24,25] The overall survival of NSCLC patients with BM is poor, reported to be 3–6 months, despite medical treatment.[26] The overall survival of the patients in this present study with BM was also poor, approximately 4 months.

Patients who are at high risk of developing BM

The delay of BM appearance is expected to improve prognosis of NSCLC patients. To achieve this, we need objective means to indicate patients at high risk for developing BM. Some studies have already been oriented towards this direction. Biologic agents like neuron specific enolase, carcinoembryonic antigen, serum sodium levels, or numerous molecular markers have been correlated with the development of BM and a shorter survival.[26–28]

Nevertheless, specific phenotypic characteristics may also serve as surrogate prognostic factors. Earlier studies correlated the presence of BM with advanced stage, NSCLC histotypes, delay of lung radiotherapy, younger age, and large tumor size.[28–32] However, few studies assessed in this regard tobacco consumption, comorbidities, CT scanner tumor characteristics, or the presence of metastases other than BMs.

Age at diagnosis

Age $<$ 60 years was shown to be associated with an increased risk of BM.[30,33,34] In this present study, younger age (60.8 ± 8.9 years) was correlated with a higher possibility of BM appearance (Table 2). However, younger patients with BM present a better performance status and longer survival, while they may tolerate aggressive treatment better and are willing to accept a higher risk of toxicity than older patients.[26,35]

Table 2 Correlation of brain metastases with patient- and disease-related features (univariate analysis)

Feature	Brain metastases		*P* χ^2 test
	No (N)	Yes (N)	
Patient-related variables			
Sex			
Male/female	108/14	35/4	0.833
Age			
Mean ± SD	66.5 ± 8.5	60.8 ± 8.9	<0.001[a]
Pack-years			
Mean ± SD	58.9 ± 31.9	75.9 ± 23.9	0.003[a]
COPD			
No/yes	68/54	21/18	0.836
Arterial hypertension			
No/yes	77/45	21/18	0.302
Diabetes mellitus			
No/yes	102/20	34/5	0.592
Coronary disease			
No/yes	98/24	34/5	0.332
Hypothyroidism			
No/yes	118/4	36/3	0.361[b]
Gastritis/ulcer			
No/yes	105/17	33/6	0.822
Other comorbidity			
No/yes	97/25	33/6	0.481
Disease-related variables			
Histotype			
Non-differentiated NSCLC	33	16	0.586[b]
Squamous	38	11	
Adenocarcinoma	48	11	
Large cell carcinoma	3	1	
Location			
Central/peripheral	105/17	33/6	0.822
Bronchoscopic findings			
Mass	29	7	0.151
Infiltration	78	31	
None	15	1	
Lung tumor side			
Right/left	62/60	22/17	0.543
Lung tumor lobe			
Upper	86	27	0.657
Middle	5	3	
Inferior	31	9	
Lung tumor size			
Mean ± SD	45.9 ± 19.3	55.1 ± 20.1	0.012[a]
Other tumor characteristics			
Pleural effusion	48	11	0.399
Cavitation	8	4	
None	66	24	
T classification (brain metastases)[c]			
T_1/T_2	10/37	3/18	0.138
T_3/T_4	22/53	2/16	
N classification (brain metastases)[c]			
N_0/N_1	29/10	9/6	0.550
N_2/N_3	53/30	17/7	
Lung metastasis			
No/yes	67/55	34/5	<0.001
Bone metastasis			
No/yes	70/52	32/7	0.005
Liver metastasis			
No/yes	91/31	33/6	0.195
Adrenal			
No/yes	91/31	35/4	0.046
Other metastasis			
No/yes	107/15	37/2	0.205

Notes: [a]Student's *t*-test; [b]Fisher's exact test; [c]TNM (tumor–node–metastasis) classification.[21]

Abbreviations: COPD, chronic obstructive pulmonary disease; NSCLC, non-small cell lung cancer; SD, standard deviation.

T and N status

T4 initial status was associated with increased risk of BM in a multivariate analysis of 305 patients with localized NSCLC.[30] The N2 status was found to be predictive of BM by Jacobs et al and by Tang et al.[36,37]

In this study, lung tumor size was correlated with the appearance of BM (55.1 ± 20.1 cm) (Table 2). This finding is in agreement with the study of Mujoomdar et al.[31] However, no correlation was found with the T status itself. T status, as well as N status, has been correlated with BM outbreak in recent studies.[30,31]

As is the case in the study of Shi et al, the authors of this present study found most of the primary tumors to be located in the right lung and in the upper lobes.[32] These frequent locations of lung tumor did not seem to correlate with the appearance of BM.[32] Central or peripheral location of primary lung tumor was not found to be correlated to BM, which is in agreement with the study of Mujoomdar et al.[31]

M status

Previous studies speculate that the spread of lung cancer to the thoracic lymphatic system and to the brain could also relate to the presence of distant metastatic disease in other organs.[31] So far, no study has confirmed this hypothesis. On the contrary, in this present study, appearance of BM was correlated with the absence of metastases in other organs, like lung, bone, and adrenal glands. Except adrenal metastases,[27] synchronous metastases in other organs have not been correlated with median survival, probably as a result of already poor prognosis of the BM.[26]

Tobacco consumption

Smoking status has already been correlated with poor prognosis and shorter overall survival in lung cancer patients,[18] but no correlation was found with BM. In this study's cohort, high tobacco consumption (75.9 ± 23.9 pack-years) was correlated with the outbreak of BM.

Table 3 Univariate analysis of brain metastases side

	Metastasis side			*P* χ^2 test
	Right (N)	Left (N)	Bilateral (N)	
Patient-related variables				
Sex				
Male/female	11/1	9/0	15/3	0.546
Age				
Mean ± SD	57.7 ± 8.3	62.6 ± 9.9	61.9 ± 8.7	0.349[a]
Pack-years				
Mean ± SD	80.8 ± 20.2	84.0 ± 19.6	68.6 ± 26.8	0.202[a]
COPD				
No/yes	6/6	5/4	10/8	1.000
Arterial hypertension				
No/yes	10/2	4/5	7/11	0.050
Coronary disease				
No/yes	12/0	9/0	13/5	0.054
Diabetes mellitus				
No/yes	11/1	9/0	14/4	0.406
Gastritis/ulcer				
No/yes	12/0	7/2	17/1	0.216
Hypothyroidism				
No/yes	12/0	6/3	15/3	0.063
Other comorbidity				
No/yes	11/1	7/2	15/3	0.740
Disease-related variables				
Histotype				
Non-differentiated NSCLC	6	2	7	0.194
Squamous	2	4	5	
Adenocarcinoma	3	3	6	
Large cell carcinoma	1	0	0	
Location				
Central/peripheral	10/2	8/1	15/3	1.000
Diagnosis to brain metastases time (weeks)				
Median (IR)	18 (4–40)	0 (0–26)	14 (0–36)	0.632[b]

Notes: [a]Analysis of variance; [b]Kruskall–Wallis test.
Abbreviations: COPD, chronic obstructive pulmonary disease; IR, interquartile range; NSCLC, non-small cell lung cancer; SD, standard deviation.

Table 4 Univariate analysis of brain metastases lobes

	Metastasis lobe		*P* Fisher's exact test
	1 lobe (N)	≥2 lobes (N)	
Patient-related variables			
Sex			
Male/female	19/2	16/2	1.000
Age			
Mean ± SD	61.0 ± 9.5	60.6 ± 8.3	0.891[a]
Pack-years			
Mean ± SD	79.1 ± 19.8	72.2 ± 28.0	0.377[a]
COPD			
No/yes	12/9	9/9	0.656[b]
Arterial hypertension			
No/yes	13/8	8/10	0.276[b]
Diabetes mellitus			
No/yes	21/0	13/5	0.015
Coronary disease			
No/yes	20/1	14/4	0.104
Hypothyroidism			
No/yes	19/2	17/1	1.000
Gastritis/ulcer			
No/yes	18/3	15/3	1.000
Other comorbidity			
No/yes	17/4	16/2	0.667
Disease-related variables			
Histotype			
Non-differentiated NSCLC	7	8	0.088
Squamous	5	6	
Adenocarcinoma	8	4	
Large cell carcinoma	1	0	
Location			
Central/peripheral	17/4	16/2	0.667
Diagnosis to brain metastases time (weeks)			
Median (IR)	17 (0–32)	8 (0–36)	0.922[c]

Notes: [a]Student's *t*-test; [b]Pearson's χ^2 test; [c]Mann–Whitney test.
Abbreviations: COPD, chronic obstructive pulmonary disease; IR, interquartile range; NSCLC, non-small cell lung cancer; SD, standard deviation.

NSCLC histological subtype

In previous studies, non-squamous lung cancer, mainly lung adenocarcinoma, showed higher prevalence of BM development.[30–32] In this study, no correlation was found between NSCLC histotype and BM appearance. This discordance is probably a result of the small number of allocated groups and the relatively large number of unspecified NSCLC tumors in the present study.

PCI

Prophylactic cranial irradiation (PCI) has been demonstrated to reduce the incidence or delay the onset of BM in patients with locally advanced NSCLC after initial treatment.[3,7,9–16] Thus, identification of risk population for BM development is pertinent. Specific phenotypes of patients at higher risk for BM development could serve as candidates of PCI and could allow early intervention, which seems more promising than the palliative approach.

Limitations

The patients in this current study were treated with sequential rather than concurrent chemoradiotherapy despite the current treatment guidelines. This limitation of the study is due to the lack of a radiotherapy department in the "Sotiria" Chest Diseases Hospital.

The pathologic data lack molecular markers, which could be related to the overall survival as is the case in many

Table 5 Correlation of brain metastases with patient- and disease-related features (multivariate analysis)

Variable	Odds ratio	95%	CI	*P*
Age	0.91	0.87	0.96	<0.001
Pack-years	1.02	1.01	1.03	0.006
Lung metastasis				
No	1.00[a]			
Yes	0.24	0.08	0.69	0.008
Bone metastasis				
No	1.00[a]			
Yes	0.30	0.11	0.81	0.018

Note: [a]Represents referral class.

recent studies. In fact, during the study period, molecular data were not available.

Implications

This study records the deleterious effect of BMs on NSCLC patient survival, enriches the high risk profile with more features, and contributes to the discussion of pathophysiologic mechanisms underlying the brain involvement in NSCLC. More studies are needed in order to elucidate these issues.

Conclusion

Younger NSCLC patients with high tobacco consumption, large tumor size, and absence of other metastases (lung, bones, adrenal metastases) are at high risk of BM appearance during the course of NSCLC and may be candidates for PCI early in the course of their disease. Apart from genome-based studies, phenotype-based studies may contribute to future lung cancer therapy.

Disclosure

The authors report no conflicts of interest in this work.

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