Original Article

Are there radiographic, metabolic, and prognostic differences between cavitary and noncavitary nonsmall cell lung carcinoma? A retrospective fluorodeoxyglucose positron emission tomography/computed tomography study

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Abstract:

AIMS: The prognosis of nonsmall cell lung cancer with cavitation (NSCLC-c) is not well-known. We compared the positron emission tomography/computed tomography (PET/CT) findings and survival data of patients with NSCLC-c patients with those without cavitation (NSCLC-nc).

METHODS: Between 7/2004 and 6/2007, cavitary lung lesions were identified in 46/248 patients undergoing fluorodeoxyglucose (FDG) PET/CT for lung nodule characterization or lung cancer staging. Within the same period, 40 of 202 patients with NSCLC-nc were randomly selected for comparison. The primary was assessed by location, size, cell type, and standardized uptake value (SUV). Disease stage was determined according to American Joint Committee on Cancer guidelines for lung cancer. Kaplan–Meier method was used for survival analysis and Cox regression to assess the effect of clinical and imaging variables on survival.

RESULTS: NSCLC-c was found in 87% of patients that had a cavitary lung lesion at PET/CT. Squamous cell carcinoma, primary size and primary-to-liver SUV ratio differed significantly between NSCLC-c and NSCLC-nc, whereas age, gender, primary location, primary SUV, type of treatment, and disease stage did not. Median survival and overall 5-year survival were 19 months and 24% for NSCLC-c, and 31 months and 31% for NSCLC-nc, $P = 0.23$. Disease stage was the only predictor of survival.

CONCLUSION: Cavitary lung lesions in patients undergoing FDG PET/CT harbor a significant risk for cancer. NSCLC-c is associated with squamous cell carcinoma, larger size, and greater FDG metabolism compared with NSCLC-nc, although these variables may not be predictive of survival. Nonetheless, PET/CT contributes to accurate staging and has an indirect impact on prognosis.

Key words:

Cavitary nonsmall cell lung cancer, fluorodeoxyglucose positron emission tomography/computed tomography, survival

Computed tomography (CT) and fluorine-18 fluorodeoxyglucose positron emission tomography (F-18 FDG PET) play an important role in the characterization of solitary pulmonary nodules and staging of nonsmall cell lung cancer (NSCLC).[1,2] The main advantage of FDG PET or PET/CT over CT is the greater diagnostic accuracy in mediastinal staging and distant metastasis detection. Particularly, FDG PET helps detect previously unsuspected metastases in as high as 37% of cases, resulting in important changes in patient management.[1,2]

Cavitary lung lesions of various etiologies may be encountered in patients undergoing

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FDG PET/CT. An accurate diagnosis remains challenging because nonmalignant cavitary lesions may mimic malignant ones on both CT and PET.[3-6] Cavitary lung cancer can be encountered in as high as 16% of primary lung cancer on CT.[3] Common radiological features of cavitary lesions suggestive of malignancy include spiculated or irregular inner and outer margins, as well as wall thickness.[3,7] Other causes of cavitary lesions include bacterial, parasitic, and invasive fungal infections, as well as Wegener granulomatosis, sarcoidosis, septic thromboembolism, pneumatoceles from prior lung injury and lung metastasis from extrapulmonary primaries.[3,8,9]

The overall 5-year survival range from 12.1% to 20.3% for NSCLC compared with 6.0% for small cell lung cancer.[10] The literature about the prognosis of cavitary NSCLC (NSCLC-c) compared with noncavitary NSCLC (NSCLC-nc) is limited to a few reports. The presence of the cavity in primary lung cancer has been associated with a worse prognosis in some reports based on radiographic exams and CT.[11-13] In other reports, however, there was no difference between cavitary lung cancer and noncavitary lung cancer.[14,15]

To elucidate further the potential relation between cavitary lesions and prognosis in patients with NSCLC, this retrospectively study compared the FDG PET/CT findings and survival between NSCLC-c and NSCLC-nc patients. We also sought to document the frequency of benign and malignant lung lesions with the cavitary feature.

Methods

Patients

Between 7/2004 and 6/2007, 248 patients underwent FDG PET/CT for characterization of solitary pulmonary nodules or staging of lung cancer at our institution. The CT images of the PET/CT studies were screened for the presence of cavitary lung lesions using the imaging archiving system SYNAPSE (Fujifilm Medical Systems, USA). Forty-six of 248 patients were found to have cavitary lung nodules. Of the remaining 202 patients without cavity, 40 patients with biopsy proven NSCLC were randomly selected for comparison. The sample tool embedded in Microsoft Excel 2003 was used for this random selection. Institutional Review Board of our institution approved this study and waived the informed consent. The deceased status was determined as of March 1, 2011, by a review of patients' charts and the Social Security Death Index.[16]

Positron emission tomography/computed tomography scanning

The patients fasted at least 4 h before the PET/CT examination and received an intravenous injection of about 5.18 MBq/kg (0.14 mCi/kg) of F-18 FDG, with a maximum of 444 MBq (12 mCi). Blood glucose concentration was <200 mg/dl immediately before the tracer injection in all studied subjects. Patients sat in a quiet injection room and were instructed not to talk during the following 60 min of the FDG uptake phase. All scans were acquired during regular breathing.

From 7/2004 to 8/2006, 72 of the 86 included patients underwent their PET/CT exam on a Gemini Scanner (Philips Medical Systems). Afterward, the remaining 14 patients underwent their exam on a Gemini TF Scanner (Philips Medical Systems). The Gemini and Gemini TF scanners have an axial co-scan range of 185 cm and 193 cm, respectively, enabling a head-to-toe imaging in one sweep. The CT consisted of 16-slice (Gemini) and 64-slice (Gemini TF) multi-detector helical CT and was performed before the PET scan. The CT data were used for generation of the CT transmission map, image fusion and anatomical correlation with the PET findings. The parameters for the CT were as follows: 120-140 kV and 33-100 mA (based on body mass index), 0.5 s per CT rotation, pitch of 0.9 and 512 × 512 matrix. No oral or intravenous contrast was administered. The PET images were acquired at 3 min per bed position for Gemini and 2-3 min per bed position for Gemini TF depending on the patient's weight.

Data analysis

PET/CT images were evaluated on a Syntegra workstation (Philips Medical Systems) by an experienced nuclear medicine physician. The lung lesions were assessed on CT for location and size (axial lesion diameter and cavity diameter) and on PET for maximum standardized uptake value (SUV). SUV was calculated using the following formula: Tissue concentration (MBq/g)/injected dose (MBq)/body weight (g). In addition, a representative SUV of the liver was obtained as an interval reference by placing a standardized 2.0 cm^3 region of interest in the mid aspect of the right hepatic lobe. The primary-liver SUV ratio was determined by dividing the SUV of the lung primary by that of the liver.

The TNM staging was based on histopathology, PET/CT findings and other imaging modalities such as brain magnetic resonance imaging, and was previously determined during the multidisciplinary lung tumor conference at our institution, according to American Joint Committee on Cancer guidelines for lung cancer, 6th edition.[17]

Statistical analysis

Patient characteristics were assessed using measures of central tendency (mean, minimum-maximum) and frequencies (%) for categorical variables. The differences of primary size, SUV, and SUV ratio between NSCLC-c and NSCLC-nc were assessed using independent Student's *t*-test or Welch's *t*-test when the variances were unequal. Chi-square tests evaluated the difference of cell type, location of the primary, type of treatment and staging. Linear regression was used to correlate SUV ratio with primary size.

Survival analysis was carried out by using Kaplan–Meier and log-rank tests. Overall survival was measured from the date of diagnosis until death from any cause. Survivors were censored on March 1, 2011, which was the time of last clinical information. Univariate proportional-hazards regression was performed to quantify the risk of death as a function of age, gender, NSCLC-c versus NSCLC-nc, primary size, SUV ratio, cell type, treatment type, and stage. Because of the small sample size and their favorable prognoses, patients with NSCLC Stages I and II were grouped together to be compared with Stage III, and Stage IV.

In a subgroup analysis, the time to death for the two most common cell types, (squamous cell carcinoma and adenocarcinoma) were each compared between NSCLC-c

and NSCLC-nc using Mann–Whitney test. A $P < 0.05$ was considered statistically significant. The statistical software MedCalc (MedCalc Software bvba, Ostend, Belgium), Version 9.3.0.0, was used.

Results

Cavitary lung lesions were present in 46 of 248 (18.5%) patients that underwent FDG PET/CT either for the characterization of a solitary pulmonary nodule or staging of lung cancer. Of these 46 patients, histopathology showed benign etiology in four patients (9%; two granulomatous inflammation, two fungal disease), small cell lung cancer in two patients (4%) and NSCLC-c in 40 patients (87%). The prevalence of NSCLC-c in our cohort was 16.1%, calculated as (40/248) × 100.

Thirty-seven of 40 (92.5%) NSCLC-c primaries and 35 of 40 (87.5%) NSCLC-nc primaries were found to have spiculated margins ($P > 0.05$). The cavity size was 1.6 ± 1.5 cm in the axial dimension in NSCLC-c group. The primary size-to-cavity size ratio was 3.2 ± 1.8 cm. Squamous cell carcinoma (45.0% vs. 17.5%), primary size (4.2 ± 2.8 cm vs. 2.5 ± 1.9 cm) and primary-to-liver SUV ratio (4.3 ± 2.9 vs. 3.2 ± 2.2) differed significantly between NSCLC-c and NSCLC-nc ($P < 0.05$) whereas age, gender, primary location, primary SUV, type of treatment and disease stage did not [Table 1]. NSCLC-c was overall larger with higher metabolic activity (primary-to-liver SUV ratio) and was associated with squamous cell carcinoma compared with NSCLC-nc, which was associated with adenocarcinoma [Figures 1 and 2].

In subgroup analyses, the larger size noticed in NSCLC-c compared to NSCLC-nc was mainly attributed to squamous cell carcinoma (5.8 ± 3.4 cm vs. 2.1 ± 0.6 cm, $P = 0.01$) and not to the adenocarcinoma (2.8 ± 1.1 cm vs. 2.7 ± 2.6 cm, $P = 0.88$). Similarly, the higher primary-to-liver SUV ratio noticed in NSCLC-c was mainly attributed to squamous cell carcinoma (5.5 ± 2.4 vs. 3.0 ± 3.3, $P = 0.049$) and not adenocarcinoma (4.2 ± 3.5 vs. 3.1 ± 2.0, $P = 0.284$). Linear regressions showed no significant correlation between primary size and primary-to-liver SUV ratio in squamous cell carcinoma for both NSCCL-c and NSCLC-nc ($P > 0.05$). In adenocarcinoma, there was a moderate correlation between primary size and primary-to-liver SUV ratio in NSCLC-c ($r = 0.56$, $P = 0.03$), but no significant correlation was found in NSCLC-nc.

Table 1: Summary of clinical and PET/CT findings, as well as survival analyses

Clinical and imaging variables	Comparisons			Univariate Cox regression	
	NSCLC-c (*n* = 40) (%)	NSCLC-nc (*n* = 40) (%)	*P*	HR (95% CI)	*P*
Age	67±11	69±10	0.45	1.00 (0.98-1.03)	0.84
Gender					
Male/female	29/11	27/13	0.77	0.83 (0.48-1.43)	0.50
Locations					
Upper lobe	25 (62.5)	24 (60)	0.97	1.02 (0.6-1.69)	0.93
Right middle lobe	1 (2.5)	1 (2.5)			
Lower lobe	14 (35)	15 (37.5)			
Lesion size					
All lesions	4.2±2.8	2.5±1.9	0.02	1.04 (0.94-1.16)	0.46
Squamous cell carcinoma	5.8±3.4	2.1±0.6	0.01		
Adenocarcinoma	2.8±1.1	2.7±2.6	0.88		
Cell type					
Squamous cell carcinoma	18 (45)	7 (17.5)	0.008	0.96 (0.71-1.31)	0.80
Adenocarcinoma	15 (37.5)	19 (47.5)			
Others	7 (17.5)	14 (35)			
SUV (primary)	8.1±4.5	6.3±4.5	0.089	1.01 (0.95-1.08)	0.67
SUV ratio					
All lesions	4.3±2.9	3.2±2.2	0.046	0.71 (0.39-1.31)	0.27
Squamous cell carcinoma	5.5±2.4	3.0±3.3	0.049		
Adenocarcinoma	4.2±3.5	3.1±2.0	0.284		
Linear regression (size and SUV ratio)					
All lesions	0.44* (*P*=0.48)	0.3* (*P*=0.48)			
Squamous cell carcinoma	0.39* (*P*=0.11)	0.01* (*P*=0.98)			
Adenocarcinoma	0.56* (*P*=0.03)	0.30* (*P*=0.22)			
Staging					
I, II	16 (40)	22 (55)	0.25	1.76 (1.30-2.37)	0.0004
III	15 (37)	11 (27)			
IV	9 (23)	7 (18)			
Kaplan–Meier analysis					
Median survival (months)	19	31	0.23		
Overall 5-year survival (%)	24	31			

*Correlation coefficient. HR = Hazard ratio, N/A = Not applicable, PET/CT = Positron emission tomography/computed tomography, NSCLC-nc = Nonsmall cell lung cancer with noncavitary, NSCLC-c = Nonsmall cell lung cancer with cavitary, CI = Confidence interval, SUV = Standardized uptake value

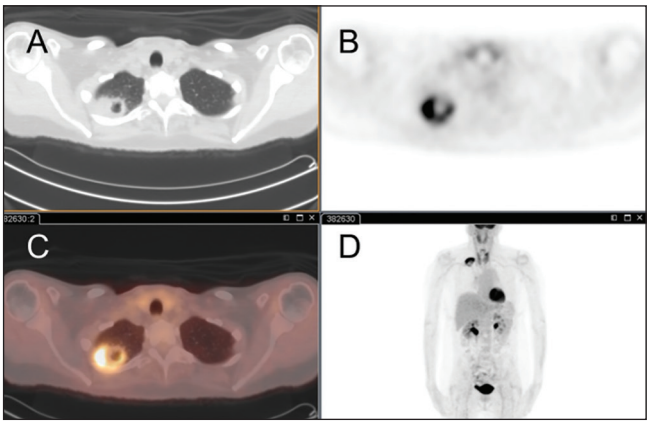

Figure 1: Cavitary nonsmall cell lung cancer. Fluorodeoxyglucose positron emission tomography-computed tomography, axial computed tomography (a), positron emission tomography (b), fused positron emission tomography-computed tomography (c), and maximum intensity projection image (d) of a 72-year-old woman with a history of squamous cell carcinoma of the right lung apex. The lesion measured 3.4 cm × 2.6 cm with a cavity of 1.5 cm, standardized uptake value of 10.9 and standardized uptake value ratio of 4.5. There was no positron emission tomography-computed tomography evidence of regional nodal or distant metastasis. The patient underwent right upper lobectomy that showed tumor invasion of the chest wall and the second rib, and the biopsy of peribronchial and hilar nodes were negative for malignancy, T4N0M0, Stage III. Chemotherapy had been planned, but she died 3 months after initial diagnosis

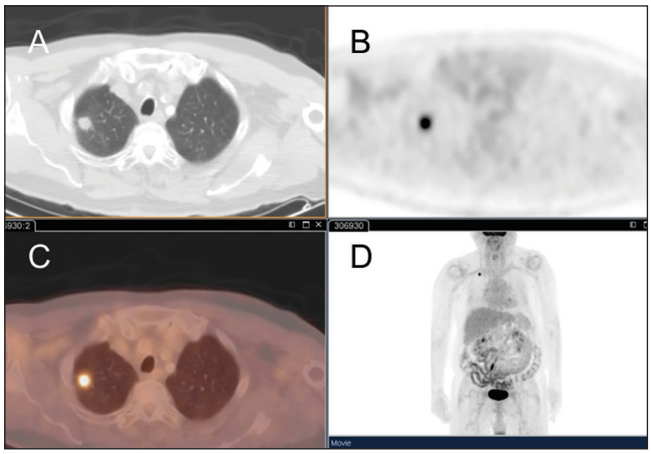

Figure 2: Noncavitary nonsmall cell lung cancer. Fluorodeoxyglucose positron emission tomography/computed tomography, axial computed tomography (a), positron emission tomography (b), fused positron emission tomography-computed tomography (c), and maximum intensity projection image (d) of a 77-year-old man with a history of adenocarcinoma of the right upper lung lobe. The lesion measured 1.6 cm × 1.4 cm with standardized uptake value of 7.6 and standardized uptake value ratio of 2.8. The patient underwent right upper lobectomy, and the biopsy of hilar nodes was negative for malignancy, T1N0M0, Stage I. He died 44 months after surgical resection of the primary

Clinical information about the treatment type was available in 38 of 40 patients with NSCLC-c and in 37 of 40 patients with NSCLC-nc. Of these, 9 NSCLC-c patients versus 11 NSCLC-nc patients had local treatment in the form of radiation treatment or surgical resection of the primary tumor; 19 versus 20 patients had combined local treatment and chemotherapy, and 10 versus 7 patients received chemotherapy as the only treatment. As a result, the treatment type was not statistically significant between NSCLC-c and NSCLC-nc ($P = 0.3$).

In a subgroup analysis, the time to death was not statistically significant in patients with squamous cell carcinoma (median: 13.3 months, range: 2.5-37.5, in NSCLC-c; median: 15.0 months, range: 1.5-57.5, in NSCLC-nc; $P = 0.56$). Similarly, the time to death in patients with adenocarcinoma did not differ significantly between NSCLC-c (median: 21.5 months, range: 8.7-41.9) and NSCLC-nc (median: 19.5 months, range: 0.9-66.3), $P = 0.72$.

Median survival and overall 5-year survival rate were 19 months and 24% for NSCLC-c and 31 months and 31% for NSCLC-nc, $P = 0.23$ [Figure 3]. The median follow-up in the 23 survivors was 61 months (range: 47-80 months). With univariate Cox proportional-hazards regression, disease stage was the only significant prognostic factor related to overall survival whereas age, gender, cell type, NSCLC-c versus NSCLC-nc, lesion size, SUV, SUV ratio, and treatment type were not [Table 1]. Thus, a multivariate Cox regression was not warranted. The hazard ratio for the stage was 1.76, indicating that patients with Stage III and Stage IV have an increased risk of dying by a factor of 1.76 and 3.09 compared to patients with combined Stage I-II.

Discussion

Fluorodeoxyglucose positron emission tomography/computed tomography findings

Cavitary lung lesions may be encountered in cancer patients undergoing FDG PET/CT. To our knowledge, there has been no report in the literature comparing the survival of NSCLC-c versus NSCLC-nc based on FDG PET/CT findings. In our PET/CT cohort, the prevalence of cavitary lung primary was 16.1%, which is consistent with previous estimates as high as 16%.[3] More than 40% of the lung primaries originated in the upper lobe, 25/40 (62.5%) for NSCLC-c and 24/40 (60%) for NSCLC-nc, which is independent of the stage at which they are diagnosed.[10,15]

As in our study, several studies have documented a larger size and a higher prevalence of squamous cell carcinoma in NSCLC-c than in NSCLC-nc.[13,14] However, we found no significant correlation between primary size and metabolic activity in squamous cell carcinoma. On the other hand, there was a moderate correlation between primary size and SUV ratio in NSCLC-c with adenocarcinoma, which seems to agree with the notion that the primary size may correlate better with SUV in adenocarcinoma than in squamous cell carcinoma.[18]

The larger size of NSCLC-c compared with NSCLC-nc has been shown to be associated with a higher rate of cell proliferation.[19] Although this does not necessarily result in a higher stage for patients with NSCLC-c as shown in our study cohort and some previous reports,[13,14] one report did indicate that NSCLC-c is associated with locally advanced and metastatic disease compared with NSCLC-nc.[15] Our findings also indicate that neither the primary size nor cell type (at least for squamous cell carcinoma and adenocarcinoma) result in a worse staging and survival.

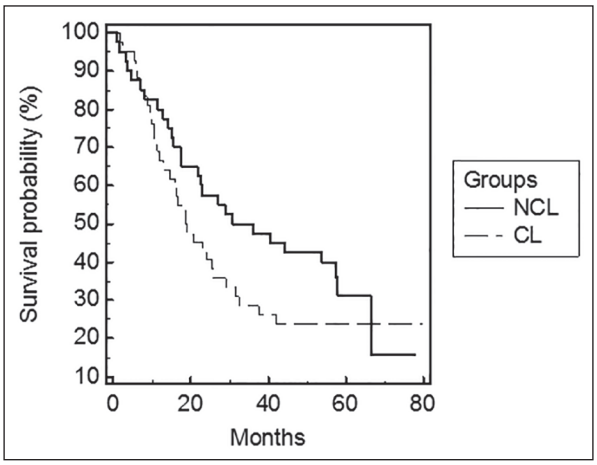

Figure 3: Kaplan–Meier survival curve of nonsmall cell lung cancer with cavitary and nonsmall cell lung cancer with noncavitary patients, $P = 0.23$

FDG PET/CT is important for the diagnosis and staging of NSCLC. A meta-analysis on the use of FDG PET showed that the primary SUV was prognostic for survival in 11 studies; however, there was no correlation between SUV and survival in two studies.[20] The incorporation of lesion SUV and SUV ratio derived from FDG PET/CT failed to correlate with survival.[21,22] SUV had no prognostic value in NSCLC in a recent study, as there was no statistically significant difference in the SUV between patients who survived at 12 months and those who had died.[23] Our findings agree with the latter reports and support the notion that the SUV may not serve well as a prognostic marker in NSCLC. As an alternative to SUV, SUV ratio was found to be statistically significant different between NSCLC-c and NSCLC-nc. It too does not indicate a survival difference between the two groups, although one report indicated that SUV ratio was a predictive marker for recurrence in Stage IA NSCLC.[24] In our opinion, the prognostic value of SUV in NSCLC is controversial and remains to be seen.

Staging and survival analyses

Several reports have shown that cavitary NSCLC may be associated with an adverse prognosis. For example, Miura *et al*.[12] found a worse prognosis for patients with cavitary adenocarcinoma. Kolodziejski *et al*.[13] found in the yet largest study of 1094 patients with Stage I-III squamous cell lung cancer that the 5-year survival was significantly shorter with NSCLC-c than NSCLC-nc (24% vs. 32%). It has been suggested that squamous cell NSCL-c may be considered a separate subentity because of the unfavorable prognosis.[13] In the current study, though the median survival and overall 5-year survival were not significantly different between the two groups (19 months and 24% for NSCLC-c vs. 31 months and 31% for NSCLC-nc, $P = 0.23$). Larger studies are required to determine the potential survival difference between cavitary and noncavitary NSCLC.

Until now, despite an active search for innovative biomarkers, the disease stage remains the most prognostic tool in NSCLC. We found that patients with Stage III and Stage IV NSCLC had an increased risk of dying by a factor of 1.76 and 3.09 compared with Stage I-II, which is consistent with recent reports. For example, Borst *et al*.[20] found a hazard ratio of 1.6 in Stage I-II versus Stage III. Sagerup *et al*.[21] found a hazard ratio of 1.54 for regional disease and 3.37 for metastatic disease in a recent study by based on 40,118 cases. Although PET/CT findings such as metabolic activity and size of the lung primary may not be good predictors of disease survival, the detection of local regional lymphadenopathy and distant metastasis is highly valuable. Thus, PET/CT contributes to accurate staging and has an indirect impact on prognostic value in NSCLC.[20,22,23]

Limitations

We acknowledge the limits of our retrospective study that contains a small number of patients in each patient group. In addition, the power to detect potential clinical and radiological differences between NSCLC-c and NSCLC-nc would have been improved by including all available instead of only 40 noncavitary NSCLC patients. Another limitation is the grouping of Stage I and II together. Given the small sample size, this grouping is necessary to allow appropriate statistical analysis. Nonetheless, our findings are consistent with previous reports on the disease prognosis. Other confounding factors, such as differences in inclusion criteria, modality of treatment and regimen of chemotherapy, as well as types of PET/CT system and acquisition protocols may have contributed to some of the disagreements between our data and those published previously.

The different PET/CT scanners used in this study may have affected the SUV measurements because of the scanners' characteristics and image reconstruction methods.[24] However, they are newer scanner systems, and the imaging protocol was comparable between the two scanners. The potential difference in SUV is probably very small and may not affect the results of the study.

Conclusion

Cavitary lung lesions in patients undergoing FDG PET/CT harbor a significant risk for cancer. NSCLC-c is associated with squamous cell carcinoma, larger size, and greater FDG metabolism compared with NSCLC-nc, although these variables may not be predictive of survival. Nonetheless, PET/CT contributes to accurate staging and has an indirect impact on prognostic value.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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