Symptom Assessment in Relapsed Small Cell Lung Cancer: Cross-Validation of the Patient Symptom Assessment in Lung Cancer Instrument

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Introduction: Lung cancer symptoms can be burdensome for patients with small cell lung cancer (SCLC). Patient Symptom Assessment in Lung Cancer (PSALC), a self-report scale for assessing SCLC symptom burden, was developed and validated previously using intravenous topotecan clinical trial data. This study cross-validates the PSALC using oral topotecan (OT) trial data.

Methods: Data were analyzed from a randomized, open-label, multicenter trial including 71 patients with relapsed SCLC receiving OT with best supportive care and 70 patients receiving best supportive care alone. PSALC and EQ-5D were administered at baseline and at 3-week intervals. Internal consistency, reliability, construct validity, and responsiveness were evaluated.

Results: Only one factor was indicated in factor analysis, hence PSALC total score (PSALC-TS) was used for psychometric analysis. Internal consistency was supported by Cronbach's alpha of 0.78. Construct validity was supported by significant associations of higher PSALC-TS (higher symptom burden) with worse Eastern Cooperative Oncology Group performance status and by correlations of PSALC-TS with EQ-5D utility index and visual analog scale score (all $p < 0.001$). Reliability was supported by intraclass correlation coefficient of 0.68 (using PSALC-TS before clinical status change) and concordance correlation coefficient of 0.69 (using PSALC-TS at baseline and before first visit). PSALC-TS was responsive to clinical status change from baseline to tumor response (responsiveness statistic = −0.99) and to tumor progression (responsiveness statistic = 0.94).

Conclusions: Consistent with prior psychometric results, this cross-validation study using OT trial data showed acceptable validity, reliability, and responsiveness of the PSALC scale, further supporting its use to measure symptom burden in previously treated SCLC.

Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancers.[1] Patients with SCLC usually experience a multitude of symptoms. Cough is the most common presenting and persistent symptom in about 75% of patients; the other common symptoms are dyspnea in about 60% of patients, chest pain in about 49% of patients, and hemoptysis in about 35% of patients. These symptoms often indicate the progression of the disease and are likely to affect patients' physical functioning and perception of the severity of their condition.[2,3]

SCLC is more aggressive than non-small cell lung cancer, metastasizes earlier and more quickly to regional and distant organ systems but is much more responsive to initial chemotherapy and radiation treatment.[1] Nevertheless, the majority of SCLC patients treated with standard first-line chemotherapy relapse after 1 year of treatment, and the prognosis for patients receiving second-line therapy is poor. Thereby, patients with SCLC may need to live with the reality of a shortened life span. The 2-year survival rate for patients with metastatic SCLC is approximately 15%.[4] For patients whose disease recurs after standard first-line platinum-based therapy, expected survival is measured in months, even with the most aggressive therapies.[5,6]

When the benefit of chemotherapy in extending life expectancy is limited, improving patients' health-related quality of life becomes an important goal of therapy. It has been shown that symptom burden and quality of life are well correlated; even in the absence of survival benefit, chemotherapy can provide palliative benefits to patients with lung cancer.[7] The association of lung cancer symptom burden and health-related quality of life warrants the assessment of lung-cancer-specific symptoms when evaluating the efficacy of a new treatment in clinical trials.

A number of instruments exist to measure lung-cancer-specific symptoms, including Lung Cancer Symptom Scale (LCSS),[8,9] Functional Assessment of Cancer Therapy—Lung (FACT-L),[10] and the European Organization for Research

and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) with Quality of Life Questionnaire Lung Cancer-13 (QLQ-LC13).[11,12] They differ in various aspects, such as symptom selection, the inclusion of global quality of life questions, type of assessment scales (i.e., visual analogue versus numerical rating scale). Although these instruments have been widely used since their introduction, they were originally validated in lung cancer populations that contain both patients with non-small cell lung cancer and also with SCLC, rather than exclusively in the population of SCLC patients. Because SCLC constitutes a minority of lung cancer cases, SCLC patients were likely underrepresented in the prior validation studies.

The Patient Symptom Assessment in Lung Cancer (PSALC) was initially developed for use in the registration trial of intravenous (IV) topotecan in treating patients with relapsed SCLC to specifically capture the symptom burden imposed on patients with SCLC, in particular among patients who failed first-line chemotherapy.[6] Using data from this prior trial, a recent publication demonstrated that the PSALC is a valid, reliable, and responsive symptom assessment questionnaire.[13]

Since its original development, the PSALC instrument has been used in over 900 patients in four multicenter clinical trials conducted in relapsed SCLC populations receiving not only the IV but also the oral formulation of topotecan. The objective of the current study is to cross-validate the PSALC instrument using the pivotal clinical trial data for oral topotecan (OT) to determine if the validity findings from the previous IV topotecan trial may also be replicated in this trial. Instrument validation is an ongoing process, such that establishing validity in additional population settings (e.g., in this study, in a subsequent clinical trial setting in relapsed SCLC) should further support the evidence base for the validity of the instrument.

MATERIALS AND METHODS

The Patient Symptom Assessment in Lung Cancer Instrument

The PSALC instrument contains nine items measuring the symptom burden experienced by patients with SCLC. It contains items related to lung-cancer-specific physical symptoms (i.e., "shortness of breath," "cough," "chest pain," "coughing up blood," "loss of appetite," "interference with sleep," "hoarseness," "fatigue") and an item related to the overall symptom burden of the disease with respect to functional status (i.e., "interference with daily activities"). According to the protocol of the clinical trial,[14] the PSALC was administered to the patients at baseline and before each subsequent clinical visit at 3-week intervals. Patients were asked to evaluate how much they had experienced each symptom (i.e., the extent to which they experienced it or were bothered by it) during the past 3 weeks on a four-point ordinal scale: 1 (not at all), 2 (a little), 3 (quite a bit), or 4 (very much). Thus, a higher score indicates greater symptom burden. Appendix shows the PSALC questionnaire.

Data Source

Data were used from an open-label, randomized, multicenter, phase III clinical trial in which OT in combination with best supportive care (BSC) (N = 71) was compared with BSC alone (N = 70) as second-line therapy for patients with relapsed SCLC. Details of the clinical trial results were published elsewhere.[14] At baseline, patients with an Eastern Cooperative Oncology Group (ECOG) score of 2 or lower, and adequate bone marrow, liver, and renal functions were recruited. It was recommended that patients receive at least four courses of OT, and the duration of the treatment depended on the tolerability and response. The primary end point of the study was overall survival (all-cause mortality). Secondary endpoints were tumor response rate, time to disease progression, symptom assessment (measured by the PSALC), quality of life evaluation (measured by the EQ-5D), and safety. Each patient's tumor response was evaluated by investigators independently as complete or partial response (CR/PR), stable disease (SD), or progressive disease (PD), according to the World Health Organization criteria. Nevertheless, because patients in the BSC alone arm were not receiving chemotherapy, it was not expected that these patients would show any response. Therefore, radiologic assessment of tumor response was only applied to patients randomized to receive OT plus BSC. The PSALC and EQ-5D were administered to patients in both treatment arms at the baseline and before each course of treatment, or approximately every 21 days.

Factor Analysis

To confirm that the PSALC contains only one factor as demonstrated in a prior validation study,[13] common factor analysis was first conducted. Using the Kaiser-Guttman rule, the number of factors was determined by the number of eigenvalues (a measure of how much of the variation in the data is accounted for by each factor) greater than one.[15–17] In addition, to estimate the contribution of each of the nine items to the factor or factors present in the instrument, final communality statistics were calculated. This step is needed to determine whether one aggregate score can be used in the validation analysis.

Internal Consistency

Three measures of internal consistency were calculated to assess the homogeneity of the scale. Pearson correlation coefficients were calculated for item-to-item correlation (between any two individual items) and item-to-total correlation (between a single item and the scale total excluding that item). In general, the threshold for a good item-to-total correlation is no lower than 0.20 to 0.40.[18,19] Cronbach's alpha coefficient reflects the average correlation among all the items in the scale. It was calculated for PSALC scores evaluated at the baseline and at four subsequent follow-up visits, separately. A "good" alpha is typically established by a value between 0.7 and 0.9.[20]

Test-Retest Reliability

The stability of a measure on the same patient from one time to another is a desirable feature of an instrument when

the underlying construct remains constant. The time period between two consecutive tests should be sufficiently short to minimize the possibility of change in the underlying construct between two assessments. This property was evaluated by test-retest reliability. Specifically, the correlation between the baseline and first-visit PSALC scores was quantified by the concordance correlation coefficient (CCC) and the intraclass correlation coefficient (ICC) were obtained for patients before any documented clinical changes in tumor response (e.g., before the first documented response for patients with an overall evaluation of CR/PR, and before the first documented progression for patients with an overall evaluation of SD, PD, or not determined [ND]), including the baseline PSALC evaluations.

Using each patient's PSALC scores at baseline and at the first clinical visit, CCC was calculated as

$$CCC = \frac{2 * \sigma_{12}}{\sigma_1^2 + \sigma_2^2 + (\mu_1 - \mu_2)^2},$$

where σ_t^1 is the variance of PSALC scores at the baseline ($t = 1$) and the first visit ($t = 2$), σ_{12} is the covariance of PSALC scores at two time points, and μ_t is the mean PSALC score at time t. The CCC estimates the concordance of the two assessments by measuring the deviation from a 45-degree line through the origin.[21]

ICC was calculated as

$$ICC = \frac{MS_B - MS_W}{MS_B + (k - 1) MS_W},$$

where MS_B is the mean square error between patients, MS_W is the mean square error within patients, and k is the mean number of PSALC evaluations per patient.[22] All PSALC scores of a patient from the period before any documented change in tumor response were used and pooled into one sample. That is, one patient could contribute multiple PSALC total scores (PSALC-TSs) to the pooled sample for the analysis. ICC estimates the proportion of the total variance in PSALC-TSs that can be explained by variation between patients as opposed to the variation within patients. The larger the ICC, the less the variation in PSALC-TSs from within patients contributes to the total variance, indicating higher stability of the PSALC over time.

Construct Validity

Multiple hypotheses were tested to evaluate the construct validity of the PSALC. The associations between PSALC scores and established measures, e.g., clinical markers or health-related quality of life, were estimated.

Using a contrasted group approach, the associations between symptom burden and clinical status were tested. Clinical status was measured by two clinical markers: the baseline ECOG performance status and the overall tumor response during the study period. It was hypothesized that better the clinical status, lower the lung cancer symptom burden. ECOG performance status was categorized as 0 (normal activity, asymptomatic), 1 (symptomatic, but fully ambulatory), and 2 (symptomatic, in bed less than 50% of

normal daytime). Therefore, higher the ECOG score was, higher the PSALC score was expected to be.

Similarly, patients' overall tumor response was classified as CR/PR, SD, and PD. It was hypothesized that patients with CR/PR had the lowest PSALC scores, patients with PD had the highest PSALC score, and patients with SD had PSALC scores falling in between. Tumor response evaluation reflected the best overall response during the course of the treatment. If a patient had more than one PSALC evaluation during the specified follow-up period, the average of the multiple PSALC scores for each individual patient was used in the analysis. Because patients treated with BSC alone were not evaluated for their tumor response per protocol, this hypothesis test was conducted only among patients treated with OT plus BSC.

The global difference in mean PSALC scores between the three ECOG performance status groups were first tested using F test. If a significant global difference was detected, a post hoc Tukey's test was conducted to test the differences between pairwise comparison groups (e.g., between ECOG = 0 and ECOG = 1 groups). A linear regression of baseline PSALC score as explained by ECOG performance status was performed to test the direction and the degree of association between lung cancer symptom burden and performance status. A significant and high degree of association, as reflected by the degree of the linear slope, would support the construct validity. Likewise, the above-described tests and regression were conducted to test the association between PSALC scores and tumor response.

In addition, the associations between changes in clinical status and changes in symptom burden were also tested. It was hypothesized that patients with improved clinical status would experience reduced symptom burden. Two specific relations were tested among the OT plus BSC group for their availability of clinical tumor response data. First, patients' PSALC scores during the specified study period were compared with the baseline to investigate whether patients with CR/PR would experience reduced symptom burden during the response period, patients with PD experience increased symptom burden during the progression period, and patients with SD have similar symptom burden during the stable period as at the baseline. Only patients with PSALC evaluations collected at the baseline and during the specified follow-up periods were included. The difference in PSALC score changes from baseline to the follow-up period was also tested between tumor response groups (i.e., CR/PR versus SD and CR/PR versus PD) using Student's t test. Second, PSALC scores evaluated at different follow-up periods (i.e., response, stable, and progression periods) within the same individual were compared to examine whether patients' symptom burden varied according to different tumor response periods. Specifically, PSALC scores evaluated during the response period were compared with the scores evaluated during the progression and stable period for patients with CR/PR. PSALC scores evaluated during the stable period were compared with scores evaluated during the progression period for patients with no documented response (i.e., SD, PD, or ND). If a patient underwent the PSALC evaluation more than once

during the specified period, the mean of the patient's PSALC scores was used in the analysis. The differences in the PSALC scores in the two relevant comparison periods were tested using paired *t* test.

The construct validity of the PSALC was further investigated by benchmarking with EQ-5D—an established and standardized preference-based instrument for use as a measure of health outcomes—to support the correlation between lung cancer symptoms and health-related quality of life.[7] The EQ-5D instrument has two parts: a three-level, five-dimension health status profile that can be converted into a single utility index and a visual analog scale (VAS), where the best health status is indicated by a score of 100 and the worst health status by 0. Pearson product-moment correlation coefficients were calculated to test whether PSALC scores were negatively correlated with EQ-5D utility index and EQ-5D VAS score.

Responsiveness

Three responsiveness indexes were calculated in this study to measure the ability of the PSALC instrument to detect clinically meaningful changes, including the effect size, standardized response mean, and responsiveness statistic (RS), defined as follows:

$$\text{Effect size} = D/SD^0$$

$$\text{Standardized response mean} = D/SD^*$$

$$RS = D/SD^\#$$

where D is raw score change, SD^0 is standard deviation of raw scores at the baseline, SD^* is standard deviation of raw score change (D), and $SD^\#$ is standard deviation of raw score change among patients with SD.

A higher RS would indicate greater sensitivity of the PSALC instrument to changes in clinical status. The sensitivity is generally considered small for a RS in the range 0.20 to 0.49, moderate for 0.50 to 0.79, and large for >0.80.[23]

The RSs were estimated for two different clinical situations among the OT plus BSC group for the availability of the tumor response measurements. First, PSALC scores evaluated during the response period were compared with those at the baseline among patients with CR/PR to estimate the responsiveness of the PSALC instrument to the improvement in the clinical status. Second, PSALC scores evaluated during the progression period were compared with those at the baseline and during stable period, respectively, among patients with no documented response (SD/PD/ND) to estimate the responsiveness of the PSALC instrument to deterioration in the clinical status.

RESULTS

Study Populations

The trial recruited 71 patients in the OT plus BSC arm and 71 patients in the BSC alone arm. Table 1 shows the demographic and baseline clinical characteristics by treatment group, along with the distribution of patients' overall evaluation of tumor response to the treatment. The two groups

TABLE 1. Demographic and Baseline Clinical Characteristics and Overall Tumor Response, by Treatment Group

	Treatment Group			
	Oral Topotecan + BSC (*N* = 71)		BSC Alone (*N* = 70)	
	N	*%*	*N*	*%*
Demographic characteristics				
Age, yrs				
Mean	59.8		58.6	
SD	9		8.2	
Range	37–76		43–79	
Gender				
Female	19	27	19	27
Male	52	73	51	73
Race				
White	70	98.6	70	100.0
Black	1	1.4	0	0.0
Baseline disease characteristics				
ECOG performance status				
0	8	11.3	6	8.6
1	44	62.0	41	58.6
2	19	26.8	23	32.9
Disease stage				
Limited	23	32.4	27	38.6
Extensive	48	67.6	43	61.4
Best response to treatment[a]				
Complete response	0	0.0	n/a	
Partial response	5	7.0	n/a	
Stable disease	31	43.7	n/a	
Progressive disease	24	33.8	n/a	
Not assessable	11	15.5	n/a	

[a] Response to treatment was not assessed in the BSC alone group.
BSC, best supportive care; ECOG, Eastern Oncology Cooperative Group.

were similar in age, gender, and race distributions and baseline ECOG scores and cancer stages. In patients treated with OT plus BSC who were evaluated for tumor response, no patient experienced CR whereas about 50% of the patients had a PR or were on stable status (5 achieved PR and 31 had SD, respectively), and about one third of the patients had disease progression (i.e., 24 patients), and the remaining 11 patients were not evaluable because of premature withdrawal from the study or because their lesion assessments were insufficient to confirm a response. In addition, no patients with CR/PR had PSALC evaluations during both the response and progression periods. Table 2 displays the distribution of responses to each PSALC item at baseline. These results show that most patients experienced no or a little bit of most of the symptom items, particularly "coughing up blood" and "hoarseness." As demonstrated in Table 3, the number of completed questionnaires (including PSALC, EQ-5D utility index and EQ-5D VAS) decreases over time in both treatment groups.

Factor Analysis

Factor analysis using baseline and on-treatment PSALC scores, respectively indicated that the instrument was

TABLE 2. Distribution of Patients' Responses to Each PSALC Item at Baseline

Symptom	N	[1] Not at All	[2] A Little	[3] Quite a Bit	[4] Very Much
Shortness of breath	136	21.3%	57.4%	17.7%	3.7%
Cough	135	17.8%	60.7%	17.8%	3.7%
Chest pain	135	50.4%	37.0%	8.9%	3.7%
Coughing up blood	136	89.0%	10.3%	0.0%	0.7%
Loss of appetite	136	47.1%	38.2%	11.8%	2.9%
Interference with sleep	135	40.7%	42.2%	13.3%	3.7%
Hoarseness	135	63.0%	25.9%	11.1%	0.0%
Fatigue	136	14.0%	47.1%	34.6%	4.4%
Interference with daily activities	136	25.7%	36.0%	29.4%	8.8%

PSALC, Patient Symptom Assessment in Lung Cancer; *N*, number of patients.

TABLE 3. Number of Completed Questionnaires at Baseline and at Subsequent Clinical Visits (up to the Last Recommended Treatment Cycle)

	Baseline	Cycle 1	Cycle 2	Cycle 3	Cycle 4
PSALC					
Oral topotecan + BSC	69	60	48	43	32
BSC alone	63	42	36	29	19
EQ-5D utility index					
Oral topotecan + BSC	69	63	53	45	33
BSC alone	68	49	39	30	22
EQ-5D VAS					
Oral topotecan + BSC	67	63	53	45	33
BSC alone	66	47	39	30	22

PSALC, Patient Symptom Assessment in Lung Cancer; BSC, best supportive care; VAS, visual analog scale.

TABLE 4. Cronbach's Alpha Coefficients, Using PSALC Total Scores Evaluated at the Baseline and the Subsequent Clinical Visits (up to the Last Recommended Treatment Cycle)

	Baseline	Cycle 1	Cycle 2	Cycle 3	Cycle 4
Sample size in cycle	132	102	84	72	51
Cronbach's alpha in sample	0.7737	0.8261	0.7607	0.7739	0.7781

In general, Cronbach's alpha between 0.7 and 0.9 is considered good.

TABLE 5. Mean PSALC Total Scores by Baseline ECOG Performance Status

ECOG Performance Status[a]	Mean PSALC Total Score	Standard Deviation	F-Test *p*
0 (N = 13)	12.31	2.29	
1 (N = 79)	16.37	3.72	0.0002
2 (N = 40)	17.58	4.35	

[a] ECOG performance status: 0 = Normal activity, asymptomatic; 1 = Symptomatic, but fully ambulatory; 2 = Symptomatic, in bed in less than 50% of normal daytime.

Only patients with both ECOG and PSALC scores at baseline were included in this analysis.

PSALC, Patient Symptom Assessment in Lung Cancer; ECOG, Eastern Oncology Cooperative Group.

measuring a single construct, as only one eigenvalue was greater than 1. Therefore, the sum of the nine item scores (the PSALC-TS) was used for the validation analysis. The item that contributed the least to the single factor was "coughing up blood," with a final communality estimate of 0.0717.

Internal Consistency

Using baseline PSALC evaluations, Pearson item-to-item correlation coefficients were statistically significant ($p < 0.05$) in most items, except for correlations between "coughing up blood" and several other items ("chest pain," "loss of appetite," "interference with sleep," "hoarseness," and "fatigue"), correlations between "chest pain" and several other items ("shortness of breath," "cough," and "hoarseness"), and the correlations between "hoarseness" and two items ("loss of appetite" and "fatigue"). Item-to-total correlations were high and significant (range, 0.42–0.69, $p < 0.01$) for all items except for "chest pain" (0.271), "coughing up blood" (0.224), and "hoarseness" (0.273). Analyses using on-treatment PSALC evaluations found similar results for item-to-item and item-to-total correlations. Table 4 shows that the Cronbach's alpha coefficient was 0.77 using baseline PSALC scores and

was greater than 0.7 (range, 0.76–0.83) using PSALC evaluations at each follow-up visit.

Test-Retest Reliability

The CCC was 0.69, indicating that PSALC-TSs at the baseline were reproducible at the first visit. The ICC was 0.68, suggesting that 68% of the total variance among PSALC-TSs is because of the variance between patients rather than variance within patients.

Construct Validity

Patients with worse performance status (i.e., higher ECOG scores) on average had greater symptom burden (i.e., higher PSALC-TSs) compared with patients with better performance status (i.e., lower ECOG scores). Specifically, the mean PSALC-TSs were 17.58, 16.37, and 12.31 for patients with ECOG scores of 2, 1, and 0, respectively ($p = 0.0002$) (Table 5). Furthermore, the post hoc Tukey test showed that the PSALC-TSs were different between score levels 0 versus 1 and 0 versus 2 ($p < 0.05$). A linear regression of the PSALC-TS on ECOG performance status at baseline generated a coefficient of 2.15 ($p = 0.0002$), indicating a high degree of positive association between ECOG performance status and lung cancer symptom burden (Figure 1).

Patients with an overall evaluation of CR/PR were found to have the lowest symptom burden on average (i.e., mean PSALC-TS = 12.68), and patients with overall evaluation of PD were found to have the highest symptom burden on average (i.e., mean PSALC-TS = 18.45), and patients with overall evaluation of SD had a mean PSALC-TS (15.26) between those of patients with CR/PR and PD ($p = 0.0077$) (see Table 6). A linear regression of the PSALC-TS on overall tumor response generated a slope of 2.96 ($p =$
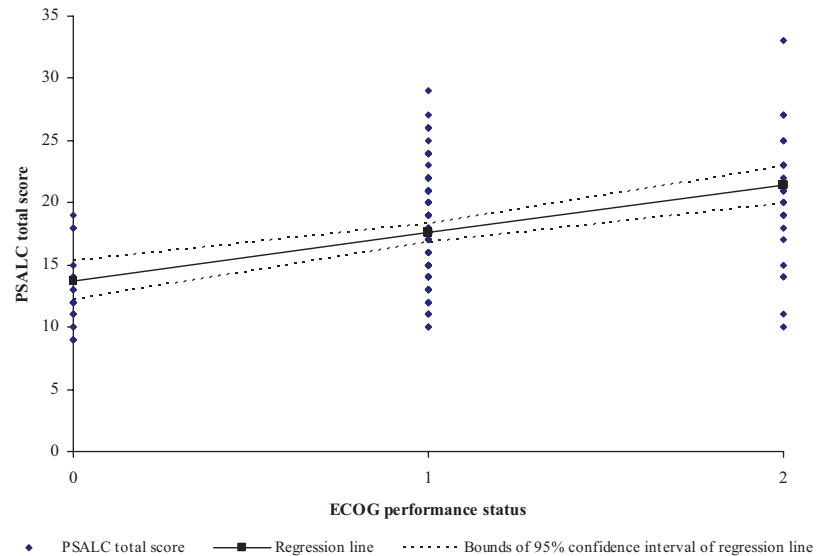
FIGURE 1. Linear association between PSALC-TS and ECOG performance status (0, 1, 2) at baseline.

• PSALC total score   ■— Regression line   ····· Bounds of 95% confidence interval of regression line

TABLE 6. Mean PSALC Total Scores by Overall Tumor Response Evaluation, for Patients Receiving Oral Topotecan Plus BSC

Tumor Response Evaluation	Mean PSALC Total Score	Standard Deviation	F Test p
CR/PR ($n = 5$)	12.68	2.46	
SD ($n = 31$)	15.26	3.07	0.0077
PD ($n = 11$)	18.45	4.89	

PSALC, Patient Symptom Assessment in Lung Cancer; BSC, best supportive care; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

0.0018), indicating a high degree of a positive association between tumor response and lung cancer symptom burden (Figure 2).

Changes in clinical status and changes in symptom burden were also found to be strongly correlated. Specifically, patients with CR/PR on average experienced a significant reduction in PSALC-TSs during response period compared with the baseline (score change = -2.43, $p = 0.0093$), patients with SD on average had similar PSALC-TSs during the stable period compared with the baseline (score change = 0.01, $p = 0.9502$), and patients with PD on average tended to experience an increase in PSALC-TSs during the progression period compared with the baseline, though the change did not reach statistical significance (score change = 2.50, $p = 0.1266$). Further, patients with CR/PR experienced a significant reduction in symptom burden from baseline to the response period compared with patients with SD ($p = 0.0016$) or PD ($p = 0.0046$) (Table 7).

Within the same individual, paired changes in PSALC-TSs and clinical status were also found. Specifically, among patients with overall evaluation of CR/PR, PSALC-TSs evaluated before tumor response were higher than their scores during the response period (13.83 versus 13.44, $p = 0.6449$), albeit not reaching statistical significance. Among patients with no documented response (SD/PD/ND), PSALC-TSs

were significantly lower during the stable period compared with their scores during the progression period (15.39 versus 17.76, $p = 0.0007$).

Patients with greater symptom burden were found to have a lower quality of life. PSALC-TSs were significantly negatively correlated with EQ-5D utility index (Pearson correlation coefficient = -0.598, $p < 0.001$, $n = 490$) and EQ-5D VAS score (Pearson correlation coefficient = -0.594, $p < 0.001$, $n = 485$), using evaluations pooled from all trial visits, and at each trial visit (Table 8). Similar results were found for correlations between EQ-5D quality of life measures and each individual PSALC item.

Responsiveness

Among patients with CR/PR, the RSs estimated by comparing PSALC-TSs evaluated during the response period with the baseline were -0.98 for effect size, -0.78 for standardized response, and -0.99 for RS. Among patients with no documented tumor response, the RSs estimated by comparing PSALC-TSs evaluated during the progression period with that at baseline were 0.58 for effect size, 0.54 for standardized response, and 1.12 for RS; the RSs estimated by comparing PSALC-TSs evaluated during progression period with those during the stable period were 0.87 for effect size, 0.94 for standardized response, and 1.11 for RS. These results suggested that the PSALC instrument is sensitive in detecting underlying changes in clinical status.

DISCUSSION

SCLC accounts for a small proportion of lung cancers and has distinctive disease characteristics compared with other types of lung cancer. Patients with SCLC usually experience detrimental lung cancer symptoms and impaired quality of life. Given that chemotherapies provide limited survival benefit, symptom relief becomes a crucial criterion in the choice of chemotherapies. Through a prior retrospective validation study using the data from the registration clinical trial of IV topotecan, the PSALC was demonstrated
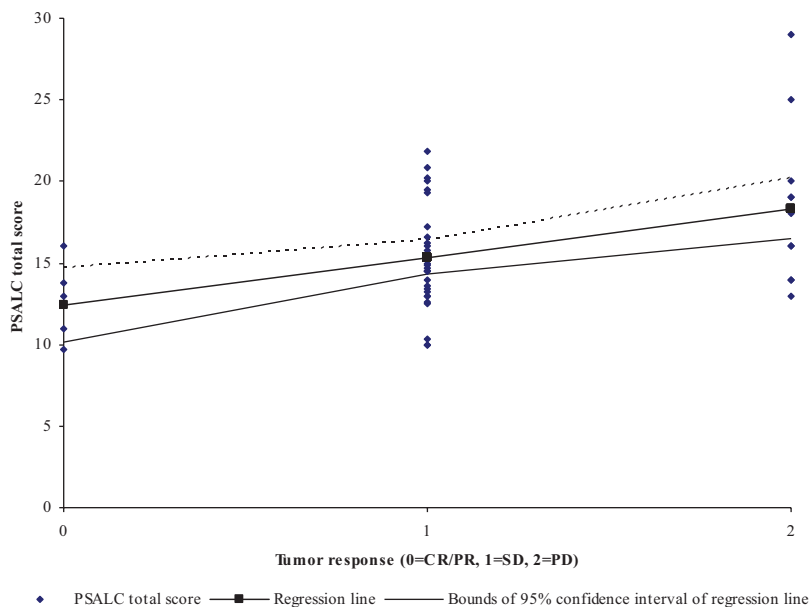
FIGURE 2. Linear association between PSALC-TS and overall tumor response evaluation (0 = CR/PR, 1 = SD, 2 = PD).

TABLE 7. Change in Mean PSALC Total Scores from Baseline to Follow-up Period, by Overall Tumor Response Evaluation, for Patients Receiving Oral Topotecan Plus BSC

	No.		Baseline		Follow-up		P^a	P^b	
	PSALC Evaluations	**Patients**	**Mean**	**Std**	**Mean**	**Std**	**(follow-up vs. baseline)**	**(CR/PR vs. SD)**	**(CR/PR vs. PD)**
Patients receiving OT + BSC									
CR/PR	14	5	15.07	1.98	12.64	2.68	0.0093		
SD	141	31	15.33	3.54	15.35	3.34	0.9502	0.0016	0.0046
PD	10	10	15.80	3.43	18.30	5.12	0.1266		

[a] Paired *t* test.
[b] Pairwise *t* test on difference in PSALC total score change between response groups.
PSALC, Patient Symptom Assessment in Lung Cancer; OT, oral topotecan; BSC, best supportive care; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; Std, standard deviation.

TABLE 8. Correlation of PSALC and EQ-5D Scores

	PSALC Total Score					
EQ-5D Measure	**All Scores**	**Baseline**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
EQ-5D utility index	-0.598^a	-0.489^a	-0.644^a	-0.694^a	-0.501^a	-0.662^a
N	490	126	101	83	69	51
EQ-5D VAS score	-0.594^a	-0.503^a	-0.645^a	-0.648^a	-0.553^a	-0.577^a
N	485	123	99	83	69	51

[a] $p < 0.001$.
PSALC, Patient Symptom Assessment in Lung Cancer.

to be a reliable, valid, and sensitive instrument.[13] The purpose of this study is to confirm the psychometric properties of the PSALC using data from the pivotal registration clinical trial for the oral formulation of topotecan.

This study replicated the previously established psychometric properties of the PSALC instrument.[13] Factor analysis showed that the PSALC instrument contains one single dimension. The item "coughing up blood" contributed the least to the single composite construct and may be measuring a somewhat different concept than the other items. Nevertheless, as in the previous study, the final communality estimate was not low enough to suggest that this item should be grouped separately from the others. The homogeneity of the PSALC was demonstrated by Cronbach's alpha coefficients greater than the 0.7 threshold for the baseline PSALC evaluation (0.77) and for PSALC evaluations from follow-up visits during the course of the clinical trial (range, 0.76–0.83), similar to the 0.78 at baseline and 0.67 to 0.79 at

follow-up visits found previously. The stability (reproducibility) of the PSALC on the same patients over time when the underlying construct remained stable was supported by test-retest reliability—CCC of 0.69 and ICC of 0.68, consistent with 0.71 and 0.61 revealed previously. The construct validity of the PSALC was supported by evaluating the association with established clinical benchmarks, ECOG performance status, and tumor response, as in the previous study, and was further enhanced by the significant correlation with EQ-5D quality of life scores which were not collected in the previous study. The responsiveness of the PSALC instrument to underlying changes in patients' tumor response status was demonstrated by the three responsiveness indexes (i.e., effect size, standardized response, and RSs) greater than 0.80. In comparison, the prior study found that the estimated RSs all fell in the small to moderate range.

This cross-validation study shares several limitations with the original validation study.[13] First, the study is limited by its retrospective study design. If feasible, a validation study on prospectively collected data could be conducted to further confirm the findings reported here. Second, the stability of the PSALC as measured by CCC (0.69) and ICC (0.68) in this study was somewhat lower than that of another well-developed lung cancer instrument LCSS validated in all lung cancer populations (Pearson correlation coefficient of 0.75).[8] Two factors might contribute to the discrepancy (1). The instruments were administered at different frequencies. In the LCSS validation study, LCSS was reevaluated 1 hour after the initial evaluation, whereas in the present clinical trial the PSALC was administered every 3 weeks between subsequent clinical visits (2). Patients' underlying condition may have changed even though it was not readily detected by tumor response evaluation, as SCLC is a progressive and deteriorative disease.

Third, the generalizability of the findings for construct validity and responsiveness is limited by the relatively small sample size that can be used for the analysis. Given that SCLC is a minority of lung cancer cases, the trial was able to enroll only 141 patients. Further, patients treated with BSC alone were not evaluated for tumor response, hence were not included for any analysis that relied on tumor response evaluation. In addition, only 5 of 71 patients on OT plus BSC achieved partial tumor response (with 31 achieving SD); however, tumor response may have been underreported as the response rate was a secondary end point of the trial. Also, for comparisons between different periods, only patients with at least one PSALC evaluation at each of the comparison periods were included. In particular, among the 24 patients with an overall tumor response evaluation of PD, only 10 patients had both a baseline PSALC evaluation and at least one PSALC evaluation available during the period of disease progression. Therefore, even though patients with PD on average tended to experience an increase in PSALC-TSs during the progression period compared with the baseline, the change did not reach statistical significance. For the same reason, even though patients with CR/PR on average tended to experience a decrease in PSALC-TSs during the response period compared with that before response, the difference did

not reach statistical significance ($n = 4$). The available data for analysis were further diminished by patient withdrawals because of adverse events, protocol violations, loss to follow-up, or various other reasons (i.e., withdrawals were 21 of 71 [30%] in OT plus BSC and 33 of 70 [37%] in BSC alone).

The findings from this cross-validation study confirm the validity of the PSALC instrument as a measure of SCLC symptoms in previously treated patients. As an instrument with only nine symptom items on an ordinal rating scale, the PSALC is feasible and easily applicable not only in formal clinical trial settings, but also in routine clinical practice. The PSALC instrument quantifies the lung cancer symptoms reported by the patients during the course of chemotherapy, and thus provides a potential tool to monitor patients' condition, in addition to clinical examination and traditional imaging.

This retrospective psychometric cross-validation analysis using clinical trial data confirms the psychometric properties of the PSALC found in a prior study and further supports the use of the PSALC instrument for measuring lung-cancer-specific symptoms in a previously treated SCLC population.

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APPENDIX

Patient Symptom Assessment in Lung Cancer Instrument

PATIENT SYMPTOM ASSESSMENT

Course Number [ ][ ] → If Course 1, please indicate the visit:
   ☐ Screening
   ☐ Prenext Course

Date of Assessment [| | |]
   Day Month Yr

Please mark one box for each symptom listed below to indicate how much you experienced that symptom during the past 3 weeks or since the last treatment.

	[1] Not at All	[2] A Little	[3] Quite A Bit	[4] Very Much
Shortness of Breath	☐	☐	☐	☐
Cough	☐	☐	☐	☐
Chest Pain	☐	☐	☐	☐
Coughing Up Blood	☐	☐	☐	☐
Loss of Appetite	☐	☐	☐	☐
Interference with Sleep	☐	☐	☐	☐
Hoarseness	☐	☐	☐	☐
Fatigue	☐	☐	☐	☐
Interference with Daily Activities	☐	☐	☐	☐