



Comparison of Symptom Score and Bronchoscopy-Based Assessment With Conventional Computed Tomography–Based Assessment of Response to Chemotherapy in Lung Cancer

abstract

Purpose There is a paucity of literature on symptom score (SS) plus fiberoptic bronchoscopy (FOB) –based response evaluation (RE) to chemotherapy for lung cancer. This study aimed to compare the reliability of RE by SS, chest radiograph (CXR), and FOB with computed tomography (CT) –based assessment (Response Evaluation Criteria in Solid Tumors (RECIST) and WHO criteria) for lung cancer chemotherapy.

Methods This was a prospective observational study involving treatment-naïve patients with lung cancer planned for chemotherapy, with one or more lesions on FOB and CT. Patients underwent assessment twice by SS, CXR, FOB, and CT (at baseline and after chemotherapy). Six symptoms (dyspnea, cough, chest pain, hemoptysis, anorexia, and weight loss) were noted on visual analog scale. Respiratory symptom burden (RSB) and total symptom burden (TSB) were calculated from the first four and all six symptoms, respectively, as the mean of individual SS. Bronchoscopic findings were recorded as per European Respiratory Society classification for tracheobronchial stenosis. Responses were classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) by each method. For FOB and SS, improvement or worsening by $\geq 20\%$ was taken as PR or PD, respectively, whereas $< 20\%$ change was considered SD. Agreements were tested using Cohen's κ statistic.

Results All individual SS, RSB, and TSB scores, and the number and distribution of FOB lesions improved significantly after chemotherapy. Individually, CXR and SS had no or minimal agreement with FOB-based and CT-based responses. RECIST and WHO criteria had strong agreement overall (Cohen's $\kappa = 0.872$) and perfect agreement for PD (Cohen's $\kappa = 1.000$). Cohen's κ values for FOB-based assessment with RECIST and WHO were 0.324 and 0.349, respectively for overall RE, and 0.462 and 0.501 for differentiating responders (CR and PR) from nonresponders (SD and PD), respectively. Cohen's κ values for PD were 0.629 (FOB alone), 0.672 (FOB and RSB), 0.739 (FOB and TSB), and 0.764 (FOB and CXR).

Conclusion CT-based assessment should remain the reference for objective RE of chemotherapy in lung cancer. A combination of FOB and CXR may be used as a surrogate to diagnose PD if CT is not feasible.

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INTRODUCTION

Computed tomography (CT) measurements of primary tumor and/or metastatic sites are commonly used for objective assessment of response to chemotherapy by RECIST and/or WHO criteria.^{1,2} In clinical practice, symptom control is also often an important consideration when making decisions regarding the continuation or discontinuation of chemotherapy.³

There is a paucity of published literature on symptom- plus bronchoscopy-based decision making for lung cancer. This study aimed to compare the reliability of response evaluation by symptom, chest radiograph (CXR), and fiberoptic bronchoscopy (FOB) –based assessment with conventional CT-based assessment for patients with lung cancer undergoing chemotherapy who had bronchoscopically-visible tumors.

METHODS

Patient Population and Treatment Details

Treatment-naïve patients with lung cancer who had at least one evaluable lesion each on FOB and CT and who were planned for initiation of chemotherapy were prospectively enrolled over a 1-year period (January 2013 to January 2014) at the authors' institute—a tertiary care referral center that caters to the population of several states in northern India. Informed consent was obtained from all patients, and the study was approved by the institutional ethics committee. At the authors' institute, all patients with lung cancer (after histologic and/or cytologic confirmation of diagnosis) are registered in the Lung Cancer Clinic. In this special clinic, managed by the faculty (DB, ANA, NS) and residents of the Department of Pulmonary Medicine, patients receive medical oncologic treatment (including chemotherapy and/or targeted therapy) as indicated and are followed up subsequent to treatment completion. The chemotherapy regimens and normal management protocols used at our center have been previously described in detail.⁴⁻⁸ In general, the standard chemotherapy regimen was a histology-guided platinum doublet with pemetrexed, docetaxel, and irinotecan being preferred nonplatinum agents for nonsquamous non-small-cell lung cancer, squamous cell carcinoma (SqCC), and small-cell lung cancer (SCLC) histologic types, respectively.

Tumors were classified histologically on the basis of morphology and relevant immunohistochemistry, as deemed appropriate, according to the

International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society classification of lung tumors.⁹ The seventh edition of the TNM classification, which is based on tumor size and extension, lymph nodal involvement, and presence of distant metastasis, was used for staging.¹⁰ Before chemotherapy initiation, demographic characteristics, including age, sex, and Karnofsky and Eastern Cooperative Oncology Group performance status, histology, disease stage, and smoking status, were noted for all patients.

Symptom and Response Assessment

Enrolled patients underwent assessment with SS, CXR, FOB, and CT scan of the thorax/upper abdomen at baseline and reassessment by all of these modalities after the third cycle of chemotherapy. Six symptoms (dyspnea, cough, chest pain, hemoptysis, anorexia, and weight loss) on a visual analog scale (VAS; 0 to 100 mm) were noted. Respiratory symptom burden (RSB) and total symptom burden (TSB) were calculated from the first four and all six symptoms, respectively, as the mean of individual SSs. The first author (LBY) was responsible for getting patients to record SSs, and he was blinded to the bronchoscopic and radiologic findings. Flexible bronchoscopy was performed under local anesthesia in the department of pulmonary medicine as per protocol described previously.¹¹ Bronchoscopic findings were recorded as per European Respiratory Society classification for tracheobronchial stenosis, from 0 (no stenosis) to 5 (> 90% obstruction).¹² Video recordings of all bronchoscopies were

Fig 1. Flow diagram as per Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines illustrating the enrolment of patients in this study. PS, performance status.

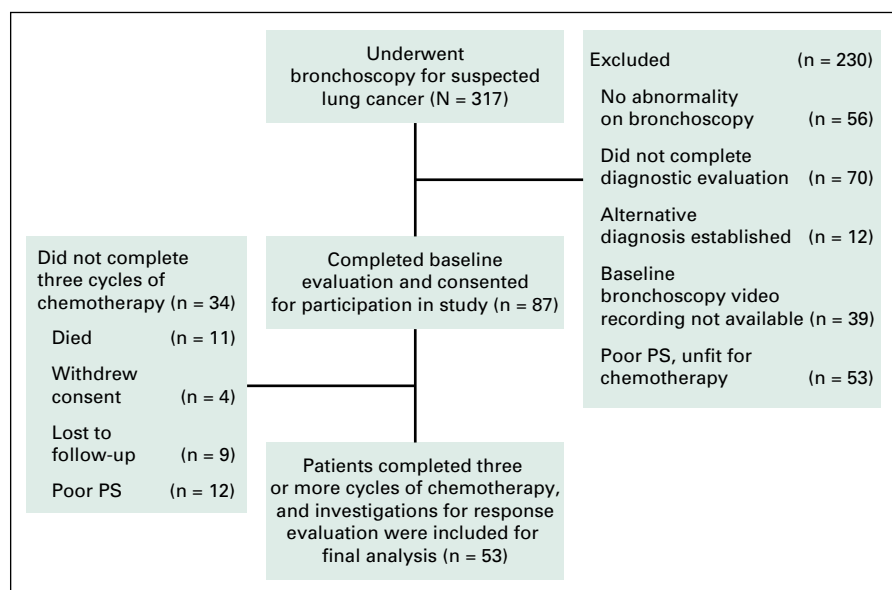


Table 1. Characteristics, Histology, and Disease Stage Profile of the Study Population (n = 53)

Baseline Characteristic	Study Population
Age, years, mean (standard deviation)	55.4 (9.3)
Male	43 (81.1)
Current or former smoker	46 (86.8)
Karnofsky performance status, %	
100	05 (09.4)
90	12 (22.6)
80	18 (34.0)
70	13 (24.5)
≤ 60	05 (09.4)
ECOG performance status	
0	06 (11.3)
1	22 (41.5)
2	17 (32.1)
3	08 (15.1)
Histology	
Squamous cell carcinoma	27 (50.9)
Adenocarcinoma	04 (07.5)
NSCLC-undiff	03 (05.7)
Small cell	19 (35.8)
T group	
T2	05 (09.4)
T3	06 (11.3)
T4	42 (79.2)
N group	
N0	03 (05.7)
N1	03 (05.7)
N2	26 (49.1)
N3	21 (39.6)
M stage	
M0	23 (43.4)
M1a	12 (22.6)
M1b	18 (34.0)
Stage	
IIIA	03 (05.7)
IIIB	20 (37.7)
IV	30 (56.6)
Extrathoracic metastasis	20 (37.7)
Small-cell lung cancer (n = 19)	
Disease stage	
Limited	08 (42.1)
Extensive	11 (57.9)

NOTE. Data are presented as No. (%) unless specified otherwise. Abbreviations: ECOG, Eastern Cooperative Oncology Group; M, presence of distant metastasis; N, lymph nodal involvement; NSCLC-undiff, undifferentiated non-small-cell lung cancer; NSCLC-NOS, NSCLC not otherwise specified; T, tumor size and extension.

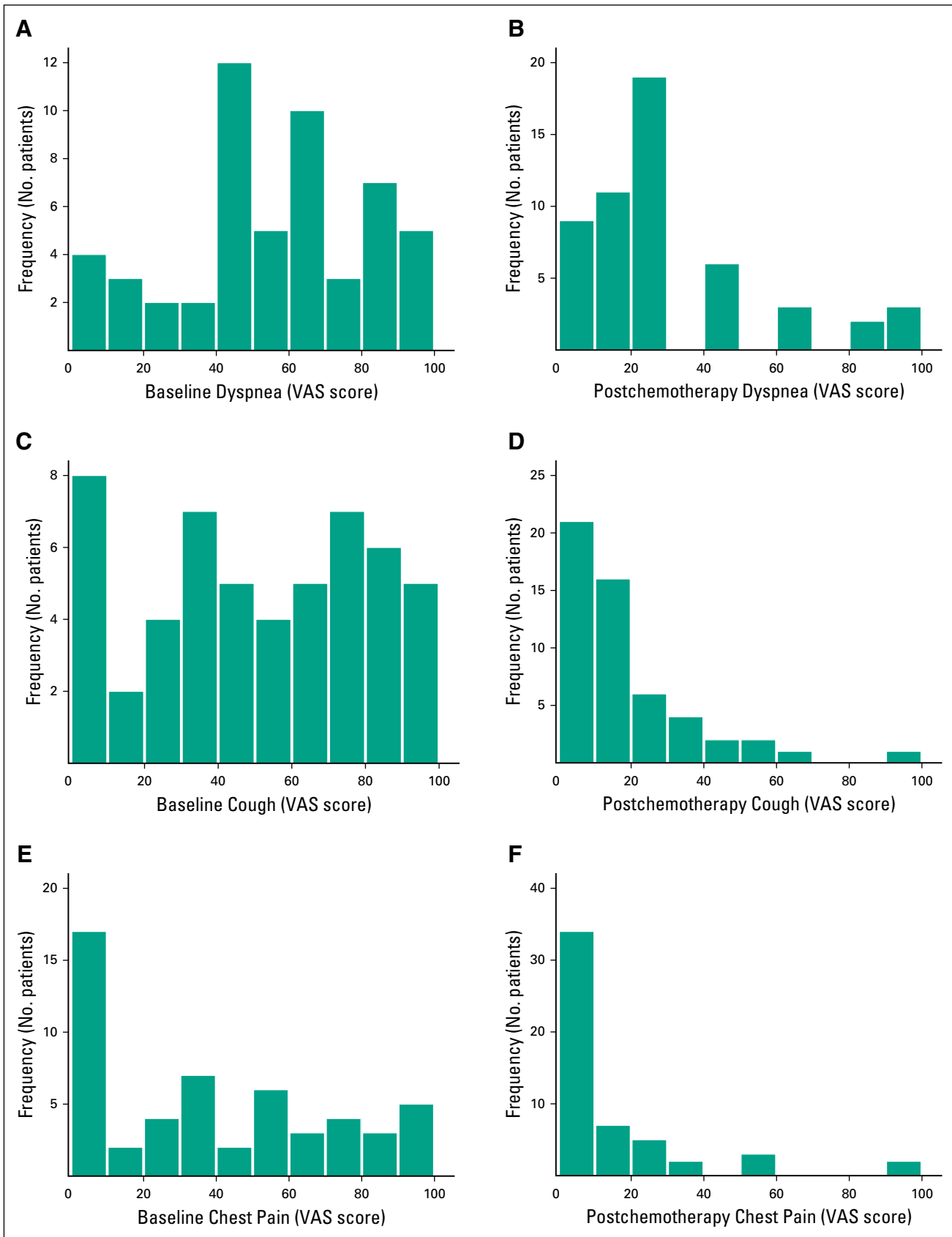
preserved for objective review and graded independently by two authors (NS and ANA), who were blinded to SSs and radiologic findings, and any disagreement was resolved subsequently by mutual discussion. In cases with more than one lesion on bronchoscopy, the lesion with the highest degree of severity was used for scoring the severity of tracheobronchial stenosis. CXR responses were assessed as per WHO criteria.² CT responses were assessed using both WHO criteria and RECIST 1.1,¹ with the latter being taken as reference standard. Patients were classified as having complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) for each of the previously mentioned methods. In the case of FOB findings and SSs, an improvement and worsening by ≥ 20% was arbitrarily taken as PR and PD, respectively, whereas a change of < 20% was considered SD.

Statistical Analysis

Data were analyzed using SPSS statistical software version 22.0 (SPSS, Chicago, IL). Descriptive data are presented as mean (standard deviation), median (interquartile range [IQR]), or percentages. Agreements between symptom, bronchoscopy, CXR, and CT response assessments were tested using Cohen's κ statistics.¹³ Wilcoxon signed rank test was used to compare changes in mean SSs (six individual symptoms, as well as RSB and TSB). Overall survival (OS) was calculated in days from date of initiation of chemotherapy to date of death or last follow-up, as applicable. Survival probability and median OS were calculated by the Kaplan-Meier method, and group differences were analyzed using the log-rank test.

RESULTS

Of 87 patients enrolled, 53 completed three or more cycles and were included for final analysis. Patient flow is depicted in Figure 1. The demographic profile of the 53 patients who enrolled in the study population is represented in Table 1. Mean (standard deviation) age was 55.4 (9.3) years; the majority (81.1%) were men and had advanced/metastatic disease (stage IV, 56.6%; stage IIIB, 37.7%) and an Eastern Cooperative Oncology Group performance status of 0 to 1 (52.8% or 2 (32.1%). SqCC (50.9%) and SCLC (35.8%) were the most common histologic types. A primary bronchoscopic lesion was most common in the left (34.0%) or the right (24.5%) main bronchus, followed by the lower one third of the trachea (15.1%) and the lobar/segmental bronchi (26.4%); its degree of mucosal obstruction/stenosis was as



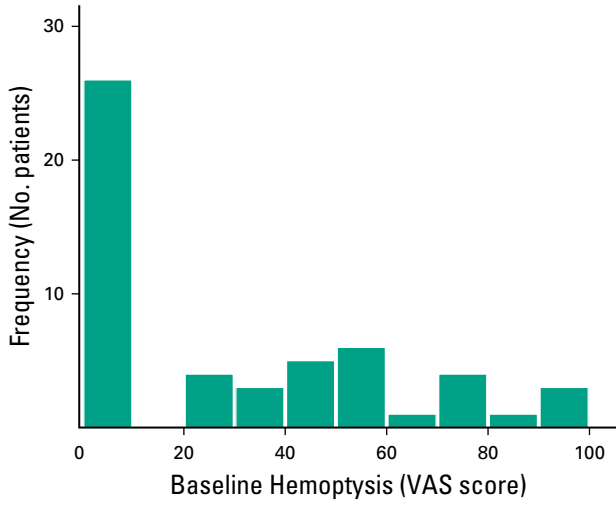
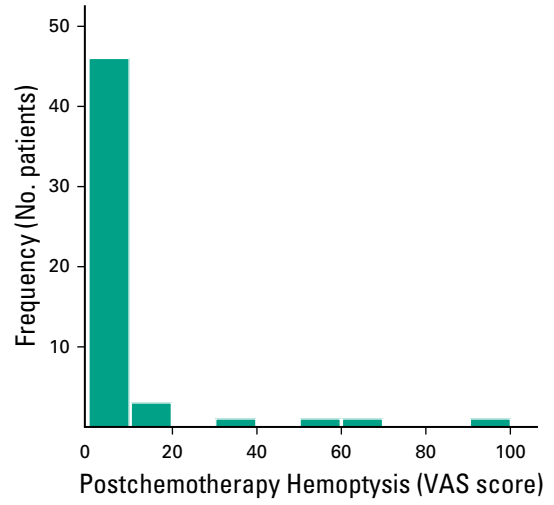
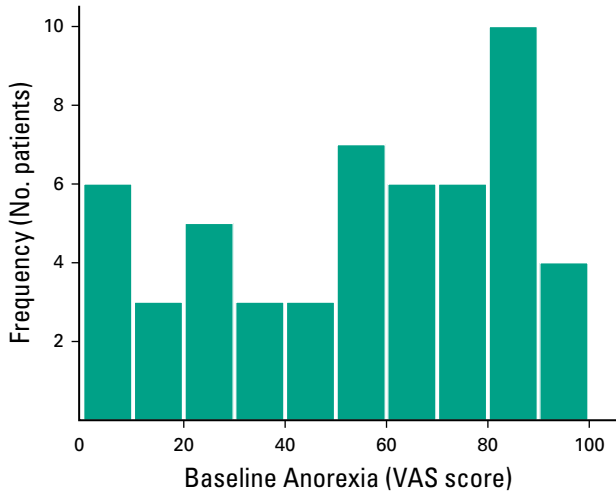
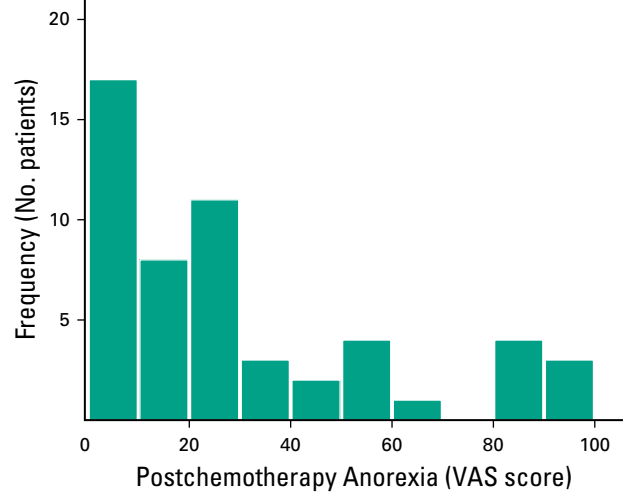
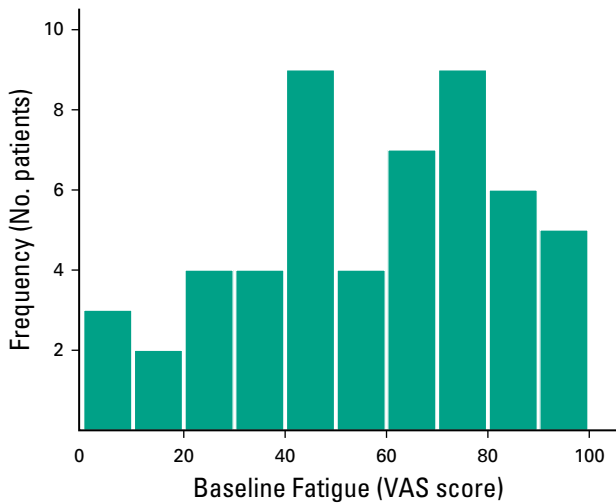
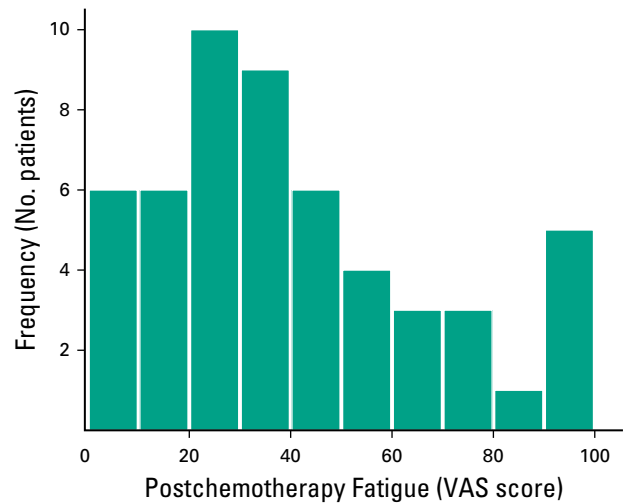
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Fig 2. Histograms illustrating the distribution of baseline and postchemotherapy symptom scores in the patient population as assessed by visual analog scale (VAS) for respiratory symptoms: (A and B) dyspnea, (C and D) cough, (E and F) chest pain, and (G and H) hemoptysis. Baseline and postchemotherapy symptom scores in the patient population as assessed by VAS for constitutional symptoms: (I and J) anorexia, and (K and L) fatigue. The horizontal axes represent the absolute value on the VAS from 0 to 100 mm, and vertical axes represent the number of patients with each value.

follows: > 90% (24.5%); 76% to 90% (18.9%); 51% to 75% (11.3%); 26% to 50% (18.9%); ≤ 25% (15.1%); and 0 (11.3%). The mean (standard deviation) number of FOB lesions at baseline was 1.7 (0.9), with 24, 11, and two patients having two, three, and four lesions, respectively.

The mean scores of all six individual symptoms, RSB, and TSB (Figs 2 and 3) showed statistically significant improvement after chemotherapy. The mean change in VAS scores after chemotherapy was 24.7 mm for dyspnea; 31.4 mm for cough; 25.5 mm for chest pain; 22.5 mm for hemoptysis; 25.4 mm for anorexia; 15.9 for weight loss; 25.7 mm for RSB; and 24.2 mm for TSB, with a P value < .001 for each comparison. The mean number, as well as the distribution, of FOB lesions decreased significantly after chemotherapy (Fig 4). CXR response had poor agreement with both FOB-based (Cohen's κ = 0.069; P = .476) and CT-based (Cohen's κ = 0.208; P = .018) responses. Changes in the RSB and TSB categories had no/minimal agreement with either FOB- or CT-based responses. On the basis of RECIST, CR and PR were observed in two and 38 patients, respectively, whereas five and eight patients had SD and PD, respectively. RECIST and WHO criteria had strong agreement with each other for overall response assessment (Cohen's κ = 0.872; P < .001). Bronchoscopic assessment had minimal agreement with assessment based on RECIST (Cohen's κ = 0.324; P < .001) and WHO (Cohen's κ = 0.349; P < .001). For differentiating responders (CR and PR) from nonresponders (SD and PD), FOB-based assessment had weak agreement with assessment based on both RECIST (Cohen's κ = 0.462; P = .001) and WHO criteria (Cohen's κ = 0.501; P < .001). For differentiating disease control (CR and PR and SD) from PD, WHO criteria-based CT response had perfect agreement (Cohen's κ = 1.000; P < .001), whereas FOB-based assessment had moderate agreement (Cohen's κ = 0.629; P < .001) in comparison with RECIST. Combinations of FOB-based assessment with symptom-based assessment and/or CXR response also showed only moderate agreement (FOB and RSB, Cohen's κ = 0.672; FOB and TSB, Cohen's κ = 0.739; FOB and CXR, Cohen's κ = 0.764; P < .001 for each of the three) with CT-based assessment for detecting PD. Median OS was 372 days (95% CI, 284 to 460 days) and it differed significantly between responders and nonresponders (469 v 225 days; log-rank P < .01) on the basis of RECIST-, WHO-, and FOB-based assessments, but not on the basis of changes in RSB or TSB categories.

DISCUSSION

This study was an attempt to assess whether SS-, CXR-, and FOB-based assessment, singly or in combination, could serve reliably as an alternative to conventional CT-based assessment for response to chemotherapy in patients with lung cancer and bronchoscopically visible lesions. It is important to determine tumor responses because, as per current guidelines, two to three additional cycles (maximum, six) of the first-line chemotherapy regimen may be given to responders (CR and PR), whereas there are concerns about increasing toxicity without substantial benefit to nonresponders (SD and PD).^{14,15} In addition, those with PD may warrant a change in chemotherapy regimen (second-line drugs) and/or alternative treatment plans on the basis of histology, stage, and performance status. The presence of SqCC and SCLC (approximately 51% and 36%, respectively) as the most frequent histologic types is consistent with the enrolment criteria for this study because both are predominantly central in location, as compared with adenocarcinoma, which tends to be more peripherally located. The mean age and demographic profile of our patient population is also similar to that observed in previous epidemiologic studies at our center.¹⁶⁻¹⁹

We wish to point out that, although FOB is an invasive modality, a repeat assessment, as was performed in this study, typically has a short procedural time with a minimal complication rate because no tissue specimens are taken. Making a decision on obtaining a repeat CT scan for assessment of chemotherapy response may be difficult at times because of the presence of preexisting renal disease, contrast hypersensitivity, cisplatin-induced renal dysfunction (during chemotherapy), or the risk of developing contrast-related renal disorders (especially in elderly patients and in those with longstanding diabetes mellitus/hypertension). In addition, there are several logistic limitations in resource-constrained settings such as ours; waiting times for getting a repeat CT scan are often much longer and the cost much higher than those for a repeat FOB.^{4,5}

In this study, changes in SSSs as well as FOB-based assessment correlated poorly with CT responses, although symptomatic improvement after chemotherapy was observed in the majority of patients. The choice of using VAS for graded symptom assessment was based on another recent study in which baseline symptoms were observed to be prognostic in nature for predicting both OS and radiologic responses.²⁰ One explanation for poor

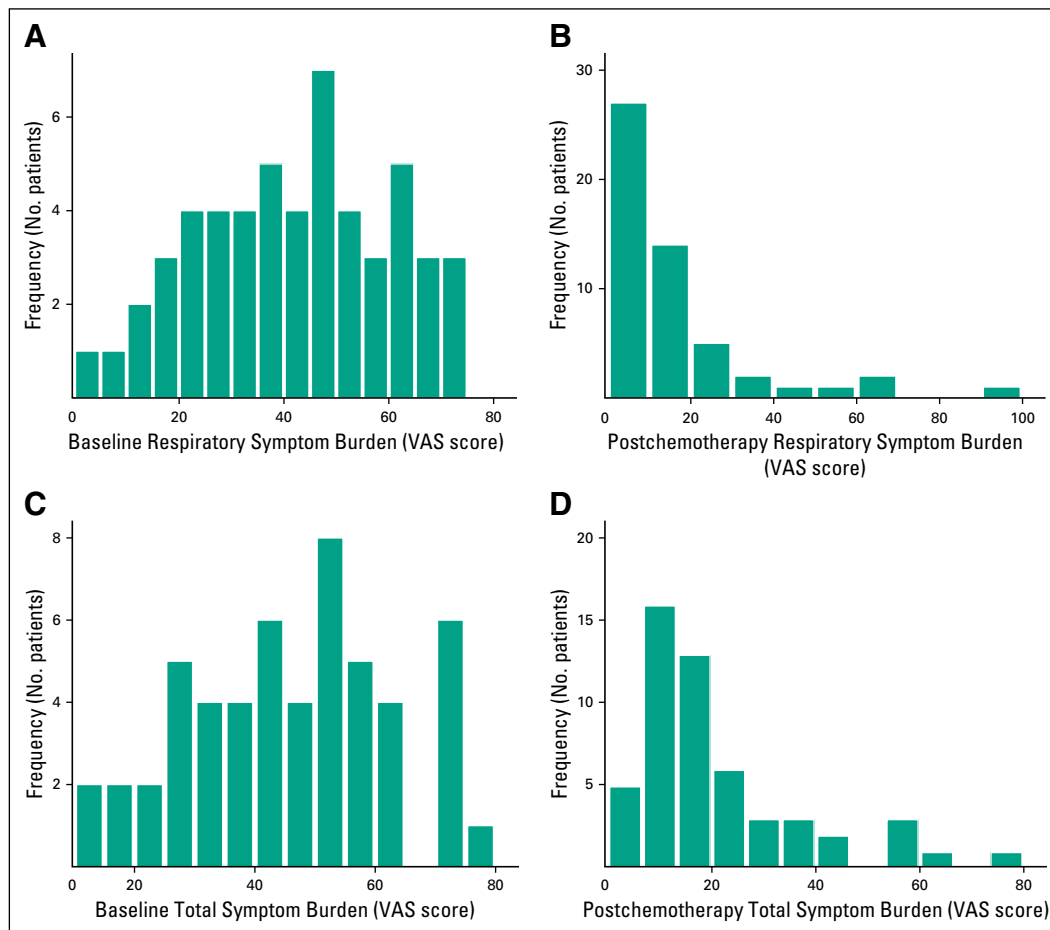


Fig 3. Histograms illustrating the distribution in the patient population of (A) baseline and (B) postchemotherapy respiratory symptom burden, and (C) baseline total symptom burden and (D) postchemotherapy total symptom burden. Respiratory symptom burden and total symptom burden were calculated from four respiratory symptoms (dyspnea, cough, chest pain, and hemoptysis) and from all six symptoms (dyspnea, cough, chest pain, hemoptysis, anorexia, and fatigue), respectively, as the mean of individual symptom scores assessed by the visual analog scale. Horizontal axes represent the absolute value on the visual analog scale from 0 to 100 mm, and vertical axes represent the number of patients with each value. VAS, visual analog scale.

agreement between FOB- and CT-based evaluations is that the former primarily assesses the intraluminal extent of tumor, whereas CT primarily assesses its extraluminal extent. Similarly, it is likely that patients experienced symptomatic benefit from chemotherapy but that the change (reduction) in size of measurable (target) lesions was not enough to fulfill the criteria for objective radiologic response.

The major limitations of this study were the small number of patients and the fact that the results may be applicable only to patients with central tumors that are visible bronchoscopically. Moreover, the inclusion criteria of bronchoscopically visible tumors led to a higher percentage of enrolled patients having SCLC histology (approximately 36%) as compared with the histologic distribution (approximately 18% to 20% SCLC) seen among patients with lung cancer as a whole.^{16,18} The fact that SCLC is more chemosensitive than other histologic types also led to a higher proportion of this study cohort having objective response rates. The nonavailability of

baseline video recordings because of technical reasons led to a few patients being excluded from enrollment; this may also have been a potential source of inadvertent selection bias in the study. Another limitation is that although both the authors who graded tracheobronchial stenosis were highly experienced in performing and interpreting bronchoscopic findings, the degree of agreement between the two observers was not formally recorded. Finally, this study only assessed the role of FOB and not that of newer bronchoscopic procedures such as endobronchial ultrasound, which has emerged as an important tool for both diagnosis and staging. These limitations notwithstanding, there are two important observations that may have applications for routine clinical practice. First, both CT-based criteria (WHO and RECIST) showed good agreement with each other and therefore, either/both may be used. Second, the combination of bronchoscopic and CXR progression may be used as a surrogate for disease progression if CT assessment is not feasible. Given the increasing role of targeted therapies in the treatment of advanced/metastatic nonsquamous

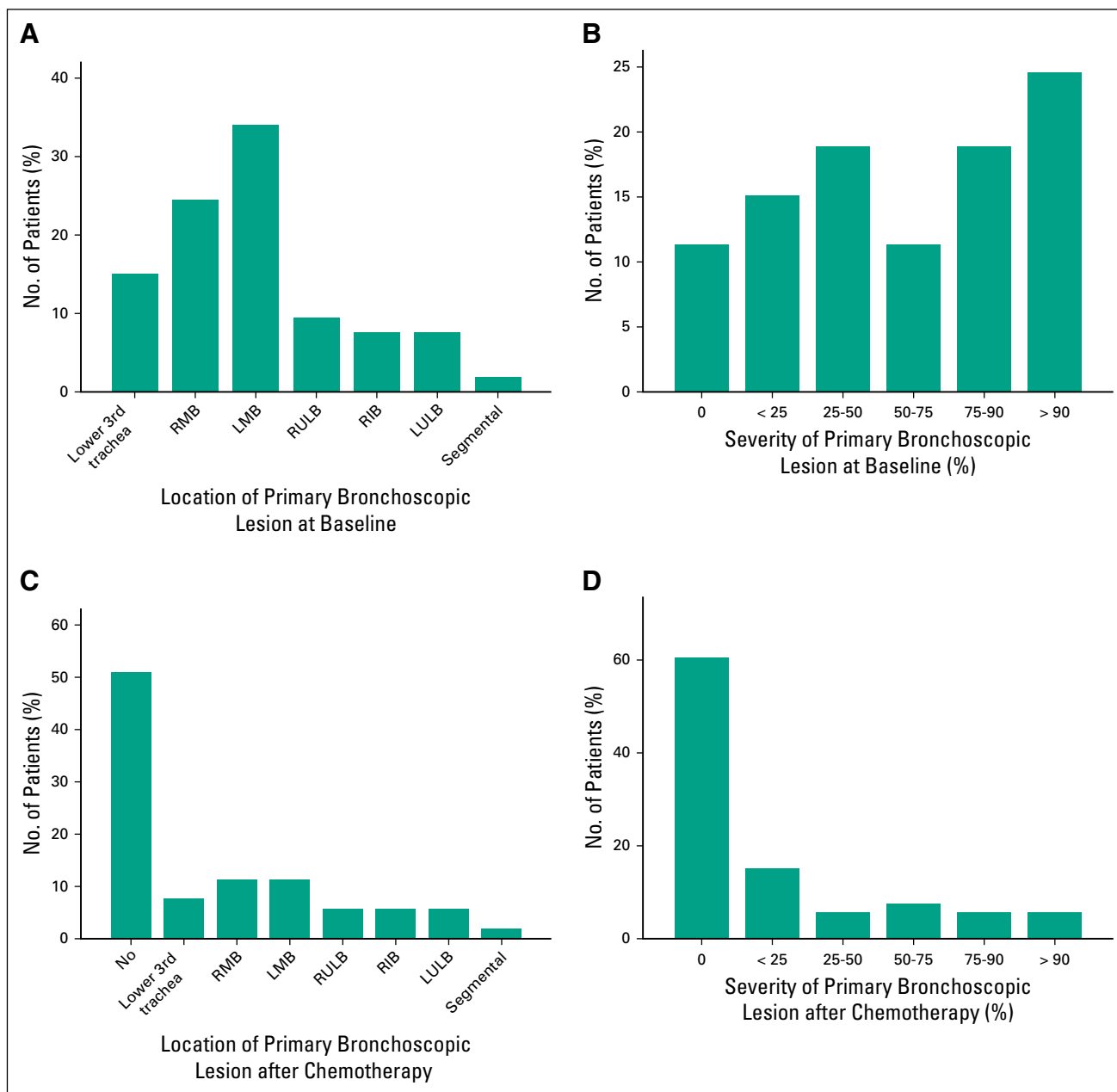


Fig 4. (A) Location and (B) severity of primary bronchoscopic lesion at baseline. (C) Location and (D) severity showed significant improvement on repeat bronchoscopic assessment after chemotherapy. LMB, left main bronchus; LULB, left upper lobe bronchus; RIB, right bronchus intermedius; RMB, right main bronchus; RULB, right upper lobe bronchus.

non-small-cell lung cancer and consequently, the emphasis on obtaining a repeat biopsy at PD both to rule out a change in histologic type and to test for actionable targets including those associated with the development of resistance to the initial agent, it could be argued that FOB could be complementary to CT for documenting PD as well as performing rebiopsy.²¹⁻²³

Previous studies comparing FOB- and CT-based assessments of response to chemotherapy were in the era before RECIST and found poor correlation (Cohen's $\kappa = 0.271$ to 0.335), with none having examined a composite of FOB, symptoms, and CXR.^{24,25} Ours is probably the first study to compare

FOB-, CXR-, and SS-based assessments, as well as their combinations, with CT-based assessment of response to chemotherapy in patients with lung cancer.

Although not a primary aim of this study and despite the small number of patients, preliminary survival data indicated that OS was significantly better for responders (CR and PR) compared with nonresponders, and this difference was apparent for assessments made on the basis of RECIST- and WHO-based CT criteria, as well as FOB-based evaluation. This also indicates that the role of FOB both to aid decision making regarding continuing or stopping chemotherapy and as a

prognostic indicator for OS deserves to be assessed further in prospective randomized trials with a greater number of patients.

In summary, the results of this prospective study indicate that CT scan–based assessment by RECIST/WHO criteria remains the reference standard for objective evaluation of patient response to chemotherapy in lung cancer.

Repeat FOB assessment for patient response to chemotherapy is not routinely indicated and should be reserved only for cases in which a repeat CT scan is not feasible and in patients in whom disease progression is suspected on CXR.

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Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I =

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