Exercise Capacity, Lung Function, and Quality of Life After Interventional Bronchoscopy

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Introduction: Malignant airway obstruction accounts for significant morbidity and mortality in patients with lung and metastatic cancer. We prospectively assessed the effects of bronchoscopic interventions for the treatment of malignant airway obstruction, with specific attention to exercise capacity and quality of life (QoL).

Methods: This is a prospective cohort study. Patients with high-grade, symptomatic central malignant airway obstruction were assessed at baseline and then at days 30, 90, and 180 after bronchoscopic intervention with spirometry, 6-minute walk test (6MWT), and QoL and dyspnea questionnaires (European Organization for Research and Treatment of Cancer Quality of Life [C30] and Lung Cancer [LC-13] modules).

Results: Thirty-seven patients were included in the final statistical analysis. Increases in 6MWT distance by 99.7 m (95% CI 33.2–166.2 m, $p = 0.002$), FEV1 by 448 ml (95% CI 203–692 ml, $p < 0.001$), and FVC by 416 ml (95% CI 130–702 ml, $p = 0.003$) were seen at day 30 compared with baseline. Clinically and statistically significant improvements were noted in composite dyspnea scores at day 30 by both QoL C30 (decrease of 39.9, 95% CI 21.4–58.4, $p < 0.001$) and LC-13 (decrease of 28.2, 95% CI 12.9–43.5, $p < 0.001$) questionnaires.

Conclusions: Bronchoscopic intervention for malignant airway obstruction is associated with improvement in 6MWT, spirometry, and dyspnea at 30 days.

Key Words: Dyspnea, Bronchoscopy, Lung cancer, Quality of life, Pulmonary function testing.

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Estimates of the incidence of central airway obstruction approach 30% in lung cancer,[1,2] with locoregional effects that may include postobstructive pneumonia, hemoptysis, atelectasis, dyspnea, and respiratory failure. Other tumors can also lead to airway compromise by direct extension or via metastasis to the airway or surrounding lymph nodes.[3]

Interventional bronchoscopy techniques have emerged in the recent years as viable palliative options in the treatment of malignant central airway obstruction. Although the technical success of such procedures has been well documented, as have short-term improvements in performance status, spirometry, and dyspnea scores, little is known regarding their impact on overall quality of life, objective measurements of functional status, and symptoms beyond the immediate postprocedure period. In addition, most studies have focused on specific interventions such as stenting, laser, or cryotherapy as opposed to an overall approach to endoscopic treatment that may often include more than one modality.

This study was designed to prospectively determine the impact of a multimodality interventional bronchoscopy approach on an objective measurement of functional status, quality of life, dyspnea, and lung function in patients with malignant airway obstruction 1, 3, and 6 months postprocedure.

PATIENTS AND METHODS

Study Design

A prospective cohort study design was used to evaluate the impact of interventional bronchoscopic techniques on patients with malignant obstruction of the central airways. The study was approved by the Conjoint Health Research Ethics Board of the University of Calgary.

Subjects

Subjects aged 18 years or older with malignant airway obstruction associated with one of the following were deemed eligible for the study: symptomatic obstruction; obstruction associated with more than 50% luminal narrowing of trachea or mainstem bronchus; or obstruction causing lower lobe or greater atelectasis. A known proven malignancy or a high suspicion of malignancy on clinical grounds was also required for study eligibility.

Subjects with a life expectancy of less than 3 months; those who refused consent; had a contraindication to bronchoscopy or anesthesia; or presented with surgically resectable lung cancer were excluded.

Patients were screened for inclusion into the study on referral to the Interventional Pulmonary Medicine Service at Foothills Medical Center, an academic tertiary care center.

Intervention

Patients received bronchoscopic treatment for malignant airway obstruction as per our standard clinical approach. Treatment modalities used in our center include mechanical debulking and dilatation with the rigid bronchoscope (Karl Storz Endoscopy Canada, Mississauga, ON; Bryan Corporation, Woburn, MA), endobronchial electrocoagulation and argon plasma coagulation (ERBOTOM ICC 350, Erbe USA, Marietta, GA), balloon bronchoplasty (CRE™ Wireguided Balloon Dilators, Boston Scientific, Natick, MA), and airway stenting (Ultraflex and Dynamic Y stents, Boston Scientific; Aero stent, Alveolus, Charlotte, NC; Tracheobronxane stent, Novatech, La Ciotat, France; Hood silicone stents, Hood Laboratories, Pembroke, MA). Brachytherapy, photodynamic therapy, and Nd:YAG laser treatments are not performed in our center.

Procedures were performed in the operating room via rigid bronchoscopy, general anesthesia, and jet ventilation. In general, extrinsic obstructions were treated with dilatation (via rigid bronchoscope or balloon bronchoplasty) and airway stenting (favoring removable devices if good response to oncological treatment/long-term survival was expected). Intrinsic obstructions were debulked with the rigid bronchoscope after electrocoagulation of the lesion, and stenting was considered in cases of recurrent disease or if additional oncologic treatment options were limited. Finally, mixed obstructions were treated with a combination of electrocoagulation and rigid bronchoscopic debulking followed by stent placement.

Patients received further chemotherapy, radiation therapy, or other treatments as recommended by their oncologist.

Outcome Measurements

Basic demographics including the subject age, gender, tumor cell type, and cancer stage were collected at baseline. Information on the location of obstruction, degree of airway patency before and after bronchoscopic intervention, and procedure-related complications were recorded, along with the specific bronchoscopic modalities used.

The primary outcome measure for this study was the change in 6-minute walk test (6MWT) from baseline. Secondary outcome measures included overall quality of life (QoL) as well as overall and dyspnea-specific symptom scales from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and lung cancer module (LC13); spirometry; pulse oximetry; resting MRC dyspnea score; modified Borg dyspnea score; and Borg dyspnea score at completion of 6MWT. Patients were evaluated at baseline and at days 30, 90, and 180. In addition to the above outcomes, airway-related complications were assessed at each visit, as well as any other oncologic treatment received. Flexible bronchoscopy was planned for all patients at 30 days after rigid bronchoscopy for endobronchial evaluation of the airway patency and assessment of interval disease progression or other complications.

Statistical Analysis

Sample size calculations based on the differences in 6MWT could not be determined as the variability of change in the walk test was not known in this patient population. This study also had an important descriptive component that was thought to be more important than the results of the 6-minute walk tests alone. Nevertheless, a sample size of 40 was selected and estimated to allow the detection of a 30 m change in 6MWT, assuming a SD of 65 m around the change (α 0.05, β 0.8).

Repeated measures analysis via a linear mixed models method and estimated margin of means was used to compare overall differences in outcomes between day 0, 30, 90, and 180. When overall significance was noted ($p \leq 0.05$), paired t tests were completed, using Bonferroni correction ($p \leq 0.05/3$), to contrast day 0 versus day 30, day 0 versus day 90, and day 0 versus day 180. All data were analyzed with the use of the SPSS software package (Version 16.0; SPSS Inc., Chicago, IL).

RESULTS

Forty subjects were initially recruited to participate in the study, with three excluded after enrolment because they failed to meet study criteria. The results of remaining 37 were analyzed. Figure 1 demonstrates the number of participants alive and having completed follow-up assessments at each scheduled time point. Mortality data were available for 36 of the 37 patients, with one patient without mortality data withdrawing from the trial after day 30 time point. Median survival for the cohort was 166 days (23.7 weeks), and 6-month survival was 46%.

Cohort demographics, tumor cell types, location, and type of obstruction in addition to history of thoracic radiation treatment and details of bronchoscopic interventions are detailed in Table 1. The majority of subjects had a diagnosis of non-small cell lung carcinoma (NSCLC); and obstruction involved large central airways (bronchus intermedius or larger) in 89% of cases. All obstructions were graded at greater than 50% luminal occlusion, with the majority (80%) being graded as between 75 and 100%.

After the bronchoscopic procedure, 34 of the 37 subjects (91.9%) had successful reestablishment of patency, which is defined as restoration of obstructed airway lumen to less than 50% obstruction.

Results of the primary and secondary outcome measures at baseline and at days 30, 90, and 180 of follow-up are summarized in Table 2. With regard to the primary outcome
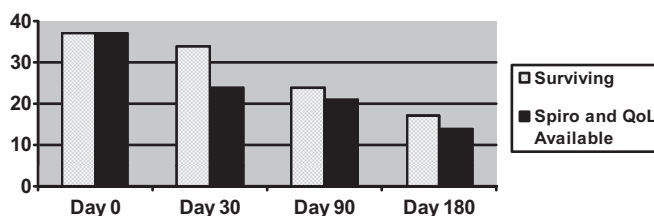

FIGURE 1. Cohort survival and available data for all time points (baseline $N = 37$).

TABLE 1. Patient Characteristics, Description of Airway Lesions, and Treatment Modalities (N = 37)

Patient Characteristics	n (%)
Mean age (yr)	62.9 (range, 25–80)
Female	21 (56.8%)
Male	16 (43.2%)
Tumour type	
Primary NSCLC	24 (64.9%)
Stage III	12 (32.4%)
Stage IV	12 (32.4%)
Primary small cell lung cancer	1 (2.7%)
Breast cancer	3 (8.1%)
Colon cancer	4 (10.8%)
Esophageal cancer	3 (8.1%)
Thyroid cancer	1 (2.7%)
Metastatic osteosarcoma	1 (2.7%)
Location of obstruction (percent of patients with obstruction)	
Trachea	12 (32.4%)
Right mainstem	16 (43.2%)
Left mainstem	11 (29.7%)
Bronchus intermedius	8 (21.6%)
Right lower lobe	3 (8.1%)
Left lower lobe	1 (2.7%)
Type of obstruction (percentage of all obstructions)	
Extrinsic	18 (35.3%)
Intrinsic	7 (13.7%)
Mixed	26 (51.0%)
Thoracic radiation therapy	
Prior history of radiation treatment	9 (24.3%)
Post-bronchoscopy radiation treatment	22 (59.5%)
Bronchoscopic modality utilized (>1 modality/subject is possible, % is proportion of cohort receiving modality)	
Electrocautery	
Electrocautery probe (soft coagulation)	19 (51.4%)
Argon plasma coagulation	3 (8.1%)
Electrocautery forceps	2 (5.4%)
Electrocautery snare	1 (2.7%)
Balloon bronchoplasty	12 (32.4%)
Airway stent	
Uncovered metal self-expandable	11 (29.7%)
Covered metal self-expandable	6 (16.2%)
Silicone (strait)	2 (5.4%)
Silicone (Y-stent)	7 (18.9%)

measure of 6MWT, statistically significant changes where noted with improvements of 99.7, 123.6, and 122.3 m from baseline at days 30, 90, and 180, respectively. At day 30, 32% of patients demonstrated an improvement in 6MWT of greater than 50 m. Statistically significant improvements at day 30 were also noted in the dyspnea scores from QLQ-C30 and LC-13 scales, resting Borg scale, FEV1, and FVC but not for overall QoL score, exercise Borg, and MRC dyspnea scales. At day 30, 48.6% (18/37), 45.9% (17/37),

and 43% (16/37) of patients demonstrated an improvement of 5 points or greater in QLQ-C30 dyspnea score, LC-13 dyspnea score, and overall QoL score, respectively. Of the 19 patients who underwent repeat flexible bronchoscopic evaluation 30 days after initial intervention, 16 (84%) maintained airway patency.

Subgroup analysis of patients who received prior radiation therapy, postprocedural radiation therapy, stage III versus stage IV non-small cell lung cancer, or those with primary lung malignancy versus metastatic disease failed to reveal statistically significant effects on any of the outcome measures. Adverse events relating to the procedure are described in Table 3. Notable adverse outcomes included development of bilateral vocal cord paralysis (in a patient with preexisting right cord paralysis due to invasive thyroid carcinoma) requiring tracheostomy and asphyxiation death of one patient secondary to occlusion of a silicone stent with tenacious secretions at day 30 postprocedure. One stent migration requiring removal the day after placement occurred while another patient also underwent removal of an airway stent between the day 30 and 90 visits because of fungal colonization and persistent secretions.

DISCUSSION

This study demonstrates the positive impact of interventional bronchoscopic procedures in patients with central malignant airway obstruction. Specifically, clinically and statistically significant improvements in 6MWT distance (our primary outcome measure) as well as in spirometry, dyspnea-specific QoL scores, and overall QoL were noted.

The 6MWT is a commonly used objective method to assess the functional status of patients with lung disease, including lung cancer,[4] and can be used to measure the response to medical interventions in patients with moderate to severe lung disease.[5] The 99.7 m mean improvement noted at the 30-day evaluation in our cohort is above the minimal clinically important difference for this test of 54 to 80 m.[6] In addition, these results compare favorably with other interventions in cancer patients. Evaluation of the effect of chemotherapy for NSCLC on 6MWT distance in a recent trial suggests that it has a tendency to remain unchanged in the majority and declined in the minority of patients, thereby reducing the group mean.[4] Although we are not aware of studies assessing the effect of radiotherapy on 6MWT, we did not detect any differences in patients who did or did not receive additional radiation treatments after bronchoscopy. These findings and the rapid (30 day) improvements noted suggest that the bronchoscopic treatments and not the additional oncologic therapy received by study subjects were responsible for the improvement.

While many reports have suggested subjective improvements in dyspnea after interventional bronchoscopy, our data confirm this improvement using objective, validated quality of life questionnaires. The improvements noted, with decreases in dyspnea scores of 28 (LC13) and 40 (C30) on 100-point scales at day 30, correlate with "moderate" to "very much" in terms of patient-perceived degree of improvement, with a change of 5 considered the minimal clinically impor-

TABLE 2. Outcome Measures at Baseline and at Days 30, 90, and 180

Measure	Day 0, Mean (SD)	Day 30 Mean, Change (95% CI)	Day 90 Mean, Change (95% CI)	Day 180 Mean, Change (95% CI)
6MWT (m)*	195.7 (161.2)	295.4, +99.7 (33.2–166.2)†	319.2, +123.6 (44.0–203.1)†	318.0, +122.3 (47.8–196.8)†
EORTC QLQ-C30*	33.3 (23.6)	42.5, +9.2 (−5.7 to 24.1)	52.6, +19.3 (6.9–31.6)†	55.0, +21.7 (4.5–38.9)†
C30 Dyspnea scale*	84.3 (21.8)	44.3, −39.9 (−58.4 to −21.4)†	36.0, −48.3 (−73.2 to −23.4)†	49.9, −34.4 (−56.5 to −12.3)†
LC13 Dyspnea scale*	61.3 (22.0)	33.1, −28.2 (−43.5 to −12.9)†	32.0, −29.3 (−44.9 to −13.6)†	35.6, −25.7 (−41.2 to −10.3)†
FEV1 (litres)*	1.283 (0.450)	1.731, +0.448 (0.203–0.692)†	1.888, +0.605 (0.339–0.870)†	1.752, +0.469 (0.214–0.724)†
FVC (litres)*	2.20 (0.785)	2.618, +0.416 (0.130–0.702)†	2.802, +0.600 (0.273–0.928)†	2.548, +0.346 (0.014–0.678)†
MRC Dyspnea*	3.88 (1.00)	3.17, −0.709 (−1.436 to 0.018)	2.71, −1.17 (−1.83 to −0.51)†	2.80, −1.08 (−1.86 to −0.30)†
Resting Borg*	2.13 (2.32)	0.82, −1.32 (−2.41 to −0.23)†	0.89, −1.24 (−2.19 to −0.30)†	0.42, −1.71 (−2.57 to −0.86)†
6MWT Borg*	3.92 (1.92)	2.58, −1.34 (−2.61 to −0.06)	2.22, −1.70 (−2.86 to −0.55)†	2.85, −1.07 (−2.41 to 0.26)†

Higher scores for European Organization for Research and Treatment of Cancer (EORTC) main module (QLQ-C30) equate to improved quality of life, while higher scores for dyspnea (C30 and lung cancer module [LC13]) equate to increased (worsened) symptoms.

  *$p < 0.05$ overall.

  †$p < 0.05$ compared with day 0.

  NS, non-statistically significant.

TABLE 3. Procedure-Related Complications

Complication	Number of Cases (% of Cohort)
Oropharyngeal minor trauma	3 (8.1)
Laryngospasm/upper airways swelling requiring brief reintubation (<12 h)	2 (5.4)
Intraoperative atrial fibrillation	1 (2.7)
Bilateral vocal cord paralysis	1 (2.7)
Pneumothorax	1 (2.7)
Stent migration	1 (2.7)
Significant stent occlusion by secretions (fatal in one patient with silicone tracheal stent, necessitated stent removal in another)	2 (5.4)

tant difference.[7] These improvements are somewhat larger than seen in another recent study using the same measurement tools, which appears to relate to a higher degree of symptomatology at baseline in this study cohort.[8]

Several authors have investigated the impact of palliative chest radiation treatment in patients with advanced lung cancer, but this information is not available specifically for a patient population such as ours with central airway obstruction. In general, while approximately one-third of patients experience improvement in dyspnea after chest radiation,[9] overall mean dyspnea scores seem to change little with treatment.[10–12] The results do appear better when radical radiation doses are administered.[13] It has been demonstrated that the addition of brachytherapy to external beam radiation therapy leads to improved mean dyspnea score, especially in a subgroup of patients with obstructive tumors, and patients with atelectasis were more likely to experience radiologic re-expansion (57 versus 35%), suggesting that endobronchial therapies beyond external beam radiation are beneficial in this patient population.[10]

In life-threatening situations, the administration of radiation alone may be problematic as effects are delayed, and there is potential for initial worsening of the obstruction secondary to tissue edema. In addition, it may be technically difficult to appropriately treat a restless patient in moderate to severe respiratory distress who cannot lie flat or is on life support. It is also known that in the case of an atelectatic lung, the longer it is present, the less likely it is to resolve with treatment.[14] The role of radiation treatment may also be limited in those previously treated or in those with relatively radio-resistant tumors such as melanoma, renal, and colon cancer.

Improvement in overall QoL scores over the course of the study was also noted in our patients, although this did not reach statistical significance at day 30. The improvement cannot be solely attributed to the bronchoscopic treatment as patients received standard supportive care and oncologic treatment. Nevertheless, most studies of chemotherapy[15,16] or palliative radiation therapy[10,11] in advanced NSCLC demonstrate stabilization or delayed decline in QoL over time, as opposed to the improvements noted in our study, again suggesting that the bronchoscopic treatments played an important role.

The improvements seen in spirometry concur with previous reports of interventional bronchoscopic techniques.[17,18] While this offers a functional rationale for the improvement in symptoms and functional status, the effect of interventional bronchoscopic techniques may extend beyond simply improving lung function. Improvement in functional status may allow for more aggressive oncologic treatment in patients initially ineligible, including curative resection in some cases.[19,20] Avoidance of additional complications resulting from airway obstruction such as hemoptysis and postobstructive pneumonia may offer additional benefit.

Despite these benefits, it is important to reflect on the significant short-term mortality with median survival just less than 6 months in our cohort, despite attempts at selecting patients with expected survival more than 90 days. While this is in keeping with other reports, it highlights the difficulty in determining prognosis in individual patients[21] and the importance of careful discussion between the medical team and patients relating to goals of care, preferences, and expectations before proceeding to an invasive palliative procedure. Patients should also be aware that minor complications are

frequent, and more severe complications including mortality can occur in relation to these procedures.

The main limitation of this study is the attrition of our cohort with time, because of both early mortality and loss to follow-up. While early mortality is simply a function of the natural history of cancer in such patients, our statistical modeling allowed us to include all patients into the analysis in an attempt to avoid a healthy survivor effect. In addition, given the observational nature of our study without a control group that did not undergo bronchoscopic intervention, a specific causal relationship between treatment and the improved outcome noted cannot be confirmed. Nevertheless, it did not appear that additional treatments influenced results in a subgroup analysis, and changes noted differed from those reported with chemotherapy or radiation therapy for lung cancer, suggesting that the bronchoscopic intervention led to the noted improvements. Finally, we limited enrolment to patients with relatively central lesions, with only 10% of subjects with lobar obstructions. As such, our results may not apply to the treatment of more distal obstructions.

The most recent ACCP Lung Cancer Guidelines make mention of several invasive approaches to palliation of dyspnea commonly used during interventional bronchoscopic procedures and recommend that malignant airway obstruction be considered in the differential diagnosis of dyspnea.[22] Our data objectively confirm the considerable benefit of interventional bronchoscopic procedures in patients with malignant airway obstruction and suggest that these techniques be considered as essential components of any multidisciplinary cancer care program.

ACKNOWLEDGMENTS

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