

## ORIGINAL ARTICLE

# Long-term quality-adjusted survival following therapeutic bronchoscopy for malignant central airway obstruction

Philip Ong, Horia B Grosu, Labib Debiane, Roberto F Casal, George A Eapen, Carlos A Jimenez, Laila Noor, David E Ost

► Additional material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2018-211521>).

Department of Pulmonary Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

## Correspondence to

Dr David E Ost, Department of Pulmonary Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA; [dost@mdanderson.org](mailto:dost@mdanderson.org)

Received 12 January 2018

Revised 28 August 2018

Accepted 3 September 2018

Published Online First

25 September 2018

## ABSTRACT

**Background** While therapeutic bronchoscopy has been used to treat malignant central (CAO) airway obstruction for >25 years, there are no studies quantifying the impact of therapeutic bronchoscopy on long-term quality-adjusted survival.

**Methods** We conducted a prospective observational study of consecutive patients undergoing therapeutic bronchoscopy for CAO. Patients had follow-up at 1 week and monthly thereafter until death. Outcomes included technical success (ie, relief of anatomic obstruction), dyspnoea, health-related quality of life (HRQOL) and quality-adjusted survival.

**Results** Therapeutic bronchoscopy was performed on 102 patients with malignant CAO. Partial or complete technical success was achieved in 90% of patients. At 7 days postbronchoscopy, dyspnoea improved (mean  $\Delta$ Borg-day-7 = -1.8, 95% CI -2.2 to -1.3,  $p < 0.0001$ ) and HRQOL improved (median prebronchoscopy 0.618 utilities, 25%–75% IQR 0.569 to 0.699, mean  $\Delta$ utility-day-7 + 0.047 utilities, 95% CI +0.023 to 0.071,  $p = 0.0002$ ). Improvements in dyspnoea and HRQOL were maintained long-term. Compared with the prebronchoscopy baseline, HRQOL per day of life postbronchoscopy improved (mean  $\Delta$ utility-long-term + 0.036 utilities, 95% CI +0.014 to 0.057,  $p = 0.002$ ). Median quality-adjusted survival was 109 quality-adjusted life-days (QALDs) (95% CI 74 to 201 QALDs). Factors associated with longer quality-adjusted survival included better functional status, treatment-naïve tumour, endobronchial disease, less dyspnoea, shorter time from diagnosis to bronchoscopy, absence of cardiac disease, bronchoscopic dilation and receiving chemotherapy.

**Conclusions** Therapeutic bronchoscopy improves HRQOL as compared with baseline, resulting in approximately a 5.8% improvement in HRQOL per day of life. The risk-benefit profile in these carefully selected patients was very favourable.

**Trial registration number** Results; NCT03326570.

Malignant central airway obstruction (CAO) occurs when tumours occlude the trachea, the main bronchi, the bronchus intermedius or a lobar bronchus. The clinical consequences of malignant CAO include dyspnoea and decreased health-related quality of life (HRQOL). Prior studies have demonstrated that therapeutic bronchoscopy for malignant CAO is associated with good short-term

## Key messages

### What is the key question?

- The long-term benefit of therapeutic bronchoscopy for malignant central airway obstruction has never been quantified in terms of quality-adjusted life-years (QALYs).
- Knowing the magnitude of the long-term benefits and what factors influence this are essential for patient management since it is central to risk-benefit assessments and determination of cost-effectiveness.

### What is the bottom line?

- Therapeutic bronchoscopy results in a 5.8% improvement in health-related quality of life per day of life, which is roughly 1.5 times the benefit seen with treatment of malignant pleural effusions over the long-term.

### Why read on?

- This manuscript quantifies the magnitude and variability of the impact of therapeutic bronchoscopy on patients with malignant central airway obstruction as measured in QALYs and identifies the factors that influence this; this information can help inform proper patient selection.

outcomes, as measured by relief of dyspnoea and improvements in HRQOL.<sup>1–14</sup>

However, while there is a single study looking at short-term changes in utility following therapeutic bronchoscopy,<sup>3</sup> and there are studies of quality-adjusted survival in other areas of interventional pulmonology such as malignant pleural effusions<sup>15</sup> and bronchoscopic treatments of emphysema,<sup>16</sup> there are to our knowledge no long-term studies of quality-adjusted survival beyond 30 days in patient treated with therapeutic bronchoscopy for malignant CAO. Quality-adjusted survival, usually expressed as quality-adjusted life-years (QALYs), is essential for cost-effectiveness analysis and has been recognised as the most important indicator of the effectiveness of healthcare interventions, as reflected by the guidelines of the National Institute of Health and Clinical Excellence, the US Public Health Service and the Agency for Healthcare Research and Quality.<sup>17–21</sup>



© Author(s) (or their employer(s)) 2019. No commercial re-use. See rights and permissions. Published by BMJ.

**To cite:** Ong P, Grosu HB, Debiane L, et al. *Thorax* 2019;**74**:141–156.

**Table 1** Patient and procedural characteristics

	Number of patients (%) N=102
Mean age (years)	63.2±11.2
Gender	
Male	65 (64%)
Female	37 (36%)
Race	
Asian	3 (3%)
Black	11 (11%)
Hispanic	11 (11%)
White	76 (75%)
Other	1 (1%)
Smoking history	
Current or prior	71 (70%)
Never	31 (30%)
Baseline Zubrod (median, IQR)	1 (1 to 2)
ASA score (median, IQR)	3 (3 to 3)
Baseline utility (median, IQR)	0.618 (0.569 to 0.699)
Baseline Borg (median, IQR)	3.5 (2 to 5)
Weeks from cancer diagnosis to procedure (median, IQR)	75 (7 to 252)
Urgency of procedure	
Elective	81 (79%)
Urgent	4 (4%)
Emergent	17 (17%)
Comorbidities*	
Asthma	3 (3%)
COPD	14 (14%)
Cardiovascular	26 (26%)
Diabetes	24 (24%)
Second primary solid tumour	11 (11%)
Increased bleeding risk	1 (1%)
Cancer type	
Lung	44 (43%)
Breast	3 (3%)
Colon	1 (1%)
Oesophageal	5 (5%)
Renal	19 (19%)
Sarcoma	3 (3%)
Other solid tumour	23 (23%)
Haematological malignancy	4 (4%)
Initial cancer treatment	
Surgery	38 (37%)
Chemotherapy	27 (27%)
Radiation therapy	13 (13%)
No treatment	24 (24%)
Prior therapeutic bronchoscopy	8 (8%)
Indication(s) for therapeutic bronchoscopy*	
Tracheoesophageal fistula	4 (4%)
Haemoptysis	21 (21%)
Malignant central airway obstruction	102 (100%)
Number of bronchopulmonary segments obstructed (median, IQR)	10 (8 to 18)

Continued

**Table 1** Continued

	Number of patients (%) N=102
Location of most proximal airway obstruction>50%	
Trachea	23 (23%)
Bilateral main stem	7 (7%)
Right main bronchus	28 (28%)
Left main bronchus	18 (18%)
Bronchus intermedius	11 (11%)
Lobar only	15 (15%)
Obstruction type	
Endobronchial	64 (63%)
Extrinsic	27 (27%)
Mixed	11 (11%)
Procedural methods	
Type of ventilation	
Jet ventilation	93 (91%)
Volume cycled	9 (9%)
Type of bronchoscopy	
Flexible only	8 (8%)
Rigid and flexible (vs flexible only)	94 (92%)
Treatment modalities used	
YAP laser	17 (17%)
Electrocautery (snare, probe or forceps)	32 (31%)
Argon plasma coagulation	64 (63%)
Cryorecanalisation	21 (21%)
Microdebrider	26 (25%)
Rigid 'coring'	11 (11%)
Dilation	20 (20%)
Stent present on completion of first procedure	34 (33%)
Stent type placed at first procedure (n=34)	
Aero	22 (65%)
Ultraflex	2 (6%)
Silicone tube	1 (4%)
Y-Stent	9 (26%)
Technical success (airway open>50%)	
Complete	68 (67%)
Partial	23 (23%)
Failed	11 (11%)
Postprocedure treatment	
Surgery	4 (4%)
Chemotherapy	60 (59%)
Radiation therapy	57 (56%)

\*Patients could have one or more comorbidities, so each comorbidity is dichotomous. For bronchoscopy indication, patients could have more than one indication for bronchoscopy, but one of them had to be for malignant central airway obstruction.

The goal of this study was to quantify long-term quality-adjusted survival following therapeutic bronchoscopy for malignant CAO. Our secondary objective was to identify factors associated with quality-adjusted survival. Our hypothesis was that therapeutic bronchoscopy would result in sustained significant long-term improvements in utility and dyspnoea as compared with baseline.

**Table 2** Factors associated with change in dyspnoea (Borg score day-7 minus Borg baseline)\*

	Univariate			Multivariate predictive			Multivariate explanatory		
	Coefficient	95% CI	P values	Coefficient	95% CI	P values	Coefficient	95% CI	P values
<b>Predictive variables</b>									
Age	0.01	−0.03 to 0.05	0.53						
Male gender	0.63	−0.27 to 1.53	0.17						
Zubrod 2-4 vs 0-1	−0.21	−1.08 to 0.67	0.64						
Baseline utility	1.04	−2.27 to 4.35	0.54						
Baseline Borg	−0.53	−0.66 to −0.40	<0.001	−0.53	−0.66 to −0.40	<0.001	−0.52	−0.64 to −0.40	<0.001
Urgent/emergent vs elective	−0.21	−1.31 to 0.89	0.71						
Time from diagnosis to procedure (weeks)	0	−0.002 to 0.002	0.89						
<b>Comorbidities</b>									
COPD	−0.42	−1.70 to 0.86	0.52						
Cardiovascular	−0.35	−1.36 to 0.66	0.49						
Diabetes	−0.21	−1.23 to 0.82	0.69						
Second primary solid tumour	0.79	−0.64 to 2.21	0.28						
<b>Cancer type</b>									
Lung	0.32	−0.57 to 1.20	0.48						
Other malignancies	<ref>								
<b>Initial treatment type</b>									
Surgery	−0.34	−1.47 to 0.79	0.55						
Chemotherapy	−0.58	−1.82 to 0.65	0.35						
Radiation therapy	−0.93	−2.55 to 0.70	0.26						
No treatment	<ref>								
Any prior therapeutic bronchoscopy	1.78	0.23 to 3.32	0.02						
<b>Indication(s) for therapeutic bronchoscopy†</b>									
Tracheoesophageal fistula	−0.05	−2.19 to 2.08	0.96						
Haemoptysis	0.61	−0.47 to 1.69	0.26						
Number of bronchopulmonary segments obstructed	−0.05	−0.13 to 0.04	0.29						
<b>Location of most proximal obstruction</b>									
Trachea	−0.83	−2.32 to 0.66	0.27						
Bilateral mainstem	−0.86	−2.85 to 1.14	0.40						
Right mainstem	−1.15	−2.57 to 0.27	0.11						
Left mainstem	−0.91	−2.47 to 0.65	0.25						
Right bronchus intermedius	−0.25	−2.04 to 1.54	0.78						
Lobar only	<ref>								
<b>Obstruction type of most proximal location</b>									
Endobronchial	<ref>								
Extrinsic	0.41	−0.61 to 1.42	0.43						
Mixed	0.71	−0.83 to 2.24	0.36						
<b>Explanatory variables</b>									
<b>Ventilation type</b>									
Jet ventilation	0.02	−1.48 to 1.53	0.97						

Continued

Table 2 Continued

	Univariate			Multivariate predictive			Multivariate explanatory		
	Coefficient	95% CI	P values	Coefficient	95% CI	P values	Coefficient	95% CI	P values
Volume cycled	<ref>								
Bronchoscopy type									
Rigid and flexible	0.27	−1.32 to 1.85	0.74						
Flexible only	<ref>								
Treatment modalities									
Any laser	−0.58	−1.73 to 0.56	0.31						
Electrocautery	−0.41	−1.34 to 0.52	0.39						
Argon plasma	0.62	−0.27 to 1.51	0.17						
Cryorecanalisation	−1.29	−2.09	0.02				−1.1	−1.88 to −0.32	0.007
Microdebrider	−0.63	−1.60 to 0.35	0.21						
Rigid 'coring'	−0.58	−1.96 to 0.79	0.40						
Dilation	0.68	−0.41 to 1.77	0.22						
Stent at first procedure	0.07	−0.87 to 1.00	0.89						
Stent type placed									
Aero	−0.45	−1.97 to 1.07	0.55						
Y-Stent	0.22	−1.40 to 1.84	0.79						
Technical success									
Complete or partial	−0.49	−1.87 to 0.88	0.48						
Failed	<ref>								
Postprocedure treatment									
Surgery	0.66	−1.50 to 2.82	0.55						
Chemotherapy	0.08	−0.81 to 0.96	0.86						
Radiation therapy	0.36	−0.52 to 1.23	0.43						

\*Day-7 Borg score is 7 days after the study entry bronchoscopy. If the patient had subsequent bronchoscopies, these were not included in this analysis.

†Patients could have one or more comorbidities, so each comorbidity is dichotomous. For bronchoscopy indication, patients could have more than one indication for bronchoscopy, but one of them had to be for malignant central airway obstruction.

## METHODS

This was a single-centre prospective observational study of consecutive patients undergoing therapeutic bronchoscopy for malignant central CAO from 1 September 2011 to 17 June 2014. Informed consent was obtained from all patients. Data were entered using definitions and quality control checks as previously described for the AQUIRE database but the data were captured using REDCap electronic data capture tools hosted at the University of Texas MD Anderson Cancer Center.<sup>22–25</sup>

Patients undergoing therapeutic flexible or rigid bronchoscopy for malignant CAO were included. CAO was defined as occlusion  $\geq 50\%$  of the trachea, mainstem bronchi, bronchus intermedius or lobar bronchus. Patients had systematic follow-up at 1 week, 1 month and monthly thereafter and were followed until death. Outcomes included: technical success (ie, relief of anatomic obstruction), dyspnoea, HRQOL/quality-adjusted survival and survival time.

Technical success was defined as reopening the airway lumen to  $>50\%$  of normal. If all stenotic airways were reopened this was considered complete success. If one or more occluded airways were reopened but any segment remained occluded this was classified as partial success. If no airways were reopened this was classified as failure. Dyspnoea was measured using the Borg score. HRQOL was measured using the SF-6D as previously described.<sup>3, 26</sup> The SF-6D provides a means to estimate a preference-based single index measure for health using general population data (see online supplement). Single index measures

such as the SF-6D generate measures of utility for particular health states that range from 0 to 1 utiles. Zero utiles represents death and one is perfect health. Quality-adjusted survival can be thought of as the area under the curve with utility on the vertical axis and time on the horizontal axis. We express quality-adjusted survival in quality-adjusted life-days (QALDs). Since the focus was on long-term outcomes and quality-adjusted survival, we report complications in the online supplement using the AQUIRE registry definitions.<sup>27</sup>

## Statistical analysis

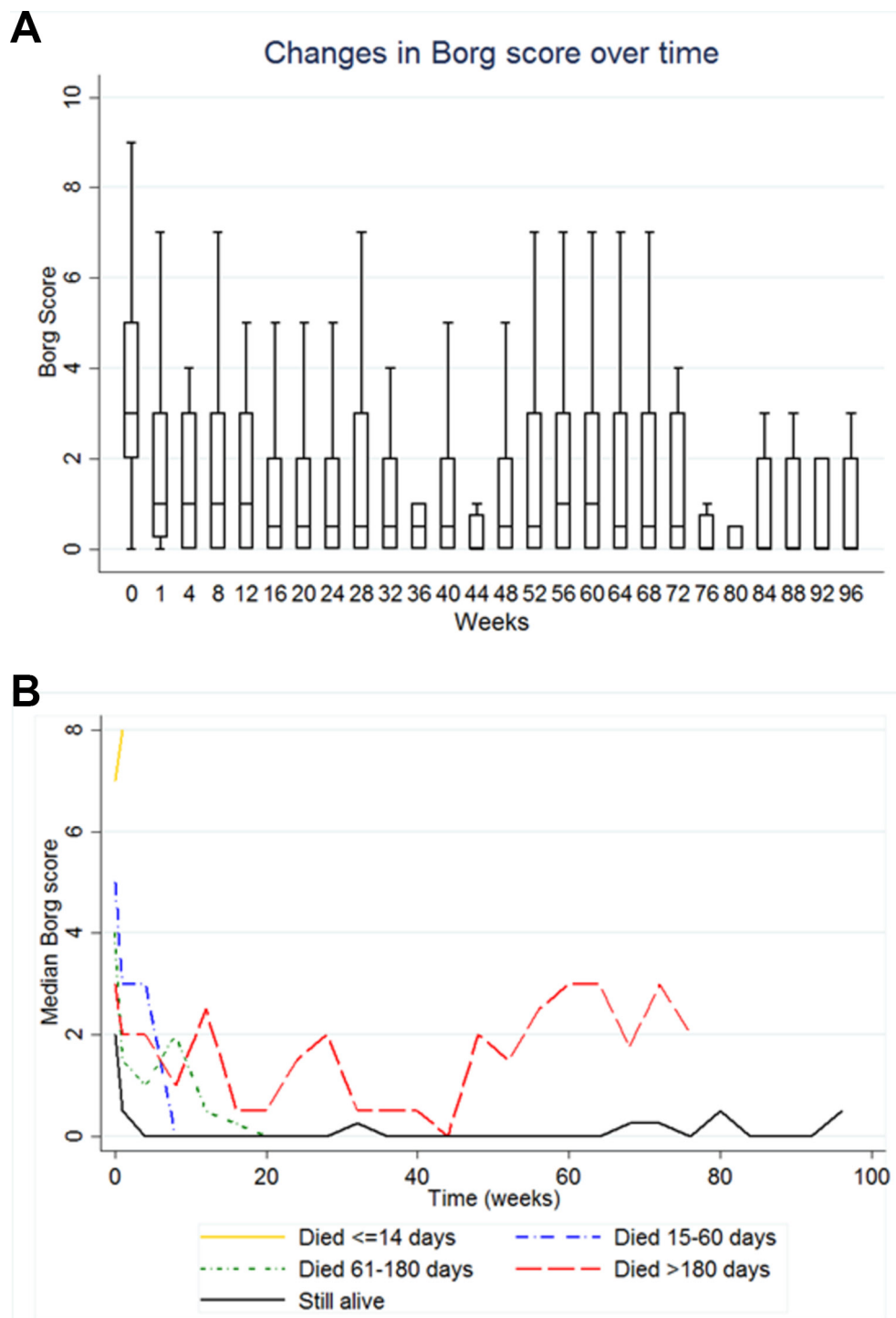
To assess the short-term impact of therapeutic bronchoscopy on HRQOL and dyspnoea, we used paired t-tests to compare baseline versus day 7 utilities (derived from SF-6D) and Borg scores. Day 7 measured from the study entry bronchoscopy. We used a generalised linear model to identify variables associated with these outcomes. The dependent variable was the pairwise difference between day 7 postprocedure scores and baseline values ( $\Delta$ utility-day-7 for HRQOL and  $\Delta$ Borg-day-7 for dyspnoea). We conducted a responder analysis for these outcomes as well (see online supplement).

The primary outcome was quality-adjusted survival and HRQOL. Long-term quality-adjusted survival was expressed as QALDs. We used a previously described method to calculate QALDs for each patient (see online supplement).<sup>15</sup> The last observation carried forward (LOCF) method was specified a priori

for imputation of missing utility measures. A secondary analysis used subsequent observations to impute missing utility measures (ie, carrying backward). There was no significant difference between results, so we report LOCF results. The Kaplan-Meier product-limit method was used to estimate median QALDs. Patients lost to follow-up or alive at study completion were censored. Cox proportional hazards models were fit to determine the association of variables with quality-adjusted survival

(see online supplement). Time-varying covariates were not used for this outcome.

To compare HRQOL over the long-term versus baseline, we defined each patient's mean HRQOL per day of life postbronchoscopy as that patient's QALD/survival time. This represents the patient's time-weighted mean utility experienced postbronchoscopy—so what was that patient's utility on an average day. We calculated the long-term change in utility ( $\Delta$ utility-long-term)



**Figure 1** Changes in dyspnoea over time for the entire cohort. (A) Boxes represent medians and IQR of Borg scores among patients alive at that time point. Note that as patients die, they no longer contribute, so median dyspnoea of those alive appears to increase (ie, sick patients with dyspnoea die and no longer contribute data as we move to the right). To adjust for this, we can stratify by survivor group (bottom panel). (B) Median Borg scores over time by survivor group.



by subtracting each patient's baseline utility from their mean HRQOL per day of life postbronchoscopy. We recognise that this is not a perfect measure of therapeutic impact, since patients who develop new clinical problems postbronchoscopy that are non-lethal could live a long time with lower utility, which would tend to drag down  $\Delta$ utility long-term. We therefore also plotted utility over time stratified by survival duration (<14, 15–60, 61–180, 181+ days).

For time to death, we used extended Cox models with time-dependent covariates to represent repeated measures such as utility and Borg scores as well as clinical events such as lower respiratory tract infections (see online supplement).

For multivariate models, all variables that had a  $p$  value <0.20 on univariate analyses were considered as candidate variables. In the absence of data on important predictors, we used backward selection to retain only variables whose  $p$  values were <0.05.  $P$  values <0.05 were considered to be significant; all tests were two-sided. Predictive models used only information available preprocedure, explanatory models used all available information.

Sample size was based on HRQOL. Assuming a baseline utility of 0.690 utilities and an improvement in utility to 0.723 utilities following therapeutic bronchoscopy with an SD of the difference of 0.1, then to have 90% power to demonstrate a difference of +0.033 utilities with an alpha of 0.05 requires 99 patients.<sup>3</sup> We estimate 10% of patients that consented would prove to have lesions that were not amenable to bronchoscopic intervention, so enrolment was capped at 110 patients. All statistical analyses were performed using STATA V.14.2 (StataCorp, College Station, Texas, USA).

## RESULTS

### Patients

A total of 102 patients had interventions. Baseline characteristics are shown in table 1. Partial or complete technical success was achieved in 90% of patients (see online supplement). Of the 102 patients, 75 died during the study period, 8 were eventually lost to follow-up (censored) and 17 were alive at study completion (censored). There were 915 scheduled follow-up measurements for dyspnoea (Borg) and utility (SF-6D) (average 9 measurements of each per patient). Follow-up data were missing in 159 (17%) time points. Of the 102 patients, 61 had one or more missing follow-up data points.

### Impact on dyspnoea

Of the 102 patients, 96 had baseline Borg scores, one was on a ventilator, two were emergent, three were missed. The analysis for dyspnoea was based on these 96 patients. Therapeutic bronchoscopy resulted in a significant improvement in dyspnoea at 7 days post the study entry bronchoscopy (mean  $\Delta$ Borg-day-7 = -1.8, 95% CI -2.2 to -1.3,  $p < 0.0001$ ). Note that lower scores indicate less dyspnoea, so if  $\Delta$ Borg-day-7 is negative dyspnoea decreased. In the multivariate predictive model, higher baseline Borg was associated with greater improvements in dyspnoea (table 2). A one unit increase in baseline Borg was associated with a 0.53 unit decrease in  $\Delta$ Borg-day-7 ( $p < 0.001$ ).

In a responder analysis, 58 of 96 patients (60%) had a clinically significant improvement in dyspnoea, 34 (35%) stayed the same and 4 (4%) worsened. In the predictive multivariate responder analysis, only higher baseline Borg ( $p < 0.001$ ) was associated with a clinically significant improvement in dyspnoea (see online supplement e-table 1). In the explanatory multivariate responder analysis, higher baseline Borg, receiving

prior cancer treatment and use of the microdebrider were associated with clinically significant improvement in dyspnoea.

This improvement in dyspnoea was sustained over time for most patients (figure 1A). Patients who died within 14 days of bronchoscopy ( $n=4$ ) did not experience dyspnoea relief. For most patients, dyspnoea initially dramatically improved and this was maintained for most of their lives (figure 1B). In some patients, towards the end of life, there was a recurrence of dyspnoea.

### Impact on HRQOL

HRQOL improved from prebronchoscopy to postbronchoscopy (median prebronchoscopy 0.618 utilities, 25%–75% IQR 0.569 to 0.699; mean  $\Delta$ utility-day-7 +0.047 utilities, 95% CI +0.023–0.071,  $p=0.0002$ ). In multivariate predictive analysis, higher baseline Borg score, not having COPD and having no prior therapeutic bronchoscopies were associated with higher  $\Delta$ utility-day-7 (ie, more benefit) (table 3). In explanatory multivariate analysis, greater improvements in dyspnoea (ie, more negative  $\Delta$ Borg-day-7), not having COPD and having no prior therapeutic bronchoscopies were associated with higher  $\Delta$ utility-day-7. A one unit increase in  $\Delta$ Borg-day-7 (ie, more dyspnoea) resulted in a decrease in  $\Delta$ utility-day-7 of 0.021 utilities ( $p < 0.001$ ).

In a responder analysis, 51 of the 102 patients (50%) had a clinically significant improvement in utility at 7 days, 33 (32%) stayed the same and 18 (18%) worsened (see online supplement e-table 2). In a multivariate predictive analysis, only having fewer lung segments occluded ( $p=0.05$ ) was associated with having a clinically significant improvement in dyspnoea. In an explanatory multivariate analysis, older age ( $p=0.03$ ), greater improvements in dyspnoea ( $p=0.01$ ) and not having COPD ( $p=0.03$ ) were associated with having a clinically significant improvement in dyspnoea.

Median quality-adjusted survival was 109 QALDs (95% CI 74 to 201 QALDs). In a predictive multivariate Cox model (table 4), factors associated with longer quality-adjusted survival included better functional status, treatment-naïve tumour, endobronchial disease and less dyspnoea at baseline. In an explanatory multivariate Cox model, these same factors were associated with longer quality-adjusted survival. In addition, shorter time from cancer diagnosis to therapeutic bronchoscopy, absence of cardiac disease, bronchoscopic dilation and receiving chemotherapy postintervention were associated with longer quality-adjusted survival.

Given that therapeutic bronchoscopy is primarily palliative, long-term impact on HRQOL per day of life is an important measure. Median postbronchoscopy HRQOL per day of life was 0.655 utilities per day (25%–75% IQR 0.590 to 0.741). Compared with the prebronchoscopy baseline, HRQOL per day of life postbronchoscopy improved (mean  $\Delta$ utility-long-term +0.036 utilities, 95% CI +0.014 to 0.057,  $p=0.002$ ). Evaluating utility changes over time stratified by survivor group (figure 2), we can see that for most survivor groups the gains in utility postbronchoscopy were maintained for some time, but as patients near the end of their lives utility starts to decrease, which in turn drags down HRQOL per day of life. Patients that died within 14 days ( $n=4$ ) were the exception; these patients had very low functional status to begin with and did not experience meaningful gains in utility. But for the majority, the immediate gains in utility postbronchoscopy were maintained for a significant amount of time.

In multivariate predictive analysis (table 5), factors associated with greater  $\Delta$ utility-long-term included higher baseline Borg score and having fewer lung segments occluded. In a multivariate

**Table 3** Factors associated with change in utility (utility at day-7 minus baseline)\*

	Univariate			Multivariate predictive			Multivariate explanatory		
	Coefficient	95% CI	P values	Coefficient	95% CI	P values	Coefficient	95% CI	P values
<b>Predictive variables</b>									
Age	0.001	-0.001 to 0.003	0.52						
Male gender	0.01	-0.04 to 0.06	0.70						
Zubrod 2-4 vs 0-1	0.036	-0.012 to 0.084	0.14						
Baseline utility	-0.014	-0.198 to 0.170	0.88						
Baseline Borg	0.013	0.004 to 0.023	0.01	0.012	0.002 to 0.022	0.015			
Urgent/emergent vs elective	0.02	-0.12	0.51						
Time from diagnosis to procedure (weeks)	-0.0001	-0.0002 to 0.0001	0.41						
<b>Comorbidities</b>									
COPD	-0.048	-0.118 to 0.023	0.18	-0.079	-0.150 to -0.008	0.03	-0.069	-0.136 to -0.002	0.05
Cardiovascular	0.015	-0.041 to 0.071	0.59						
Diabetes	0.036	-0.021 to 0.093	0.21						
Second primary solid tumour	-0.058	-0.136 to 0.020	0.14						
<b>Cancer type</b>									
Lung	0.02	-0.028 to 0.070	0.40						
Other malignancies	<ref>								
<b>Initial treatment type</b>									
Surgery	0.007	-0.057 to 0.070	0.84						
Chemotherapy	0.016	-0.052 to 0.085	0.65						
Radiation therapy	0.04	-0.044 to 0.124	0.35						
No treatment	<ref>								
Any prior therapeutic bronchoscopy	-0.125	-0.211 to -0.039	0.01	-0.111	-0.199 to -0.023	0.02	-0.102	-0.186 to -0.018	0.02
<b>indication(s) for therapeutic bronchoscopy†</b>									
Tracheoesophageal fistula	-0.074	-0.198 to 0.050	0.24						
Haemoptysis	0.007	-0.052 to 0.067	0.81						
Number of bronchopulmonary segments obstructed	-0.002	-0.006 to 0.002	0.34						
<b>Location of most proximal obstruction</b>									
Trachea	-0.019	-0.099 to 0.061	0.65						
Bilateral mainstem	-0.002	-0.114 to 0.110	0.97						
Right mainstem	0.048	-0.030 to 0.126	0.22						
Left mainstem	0.026	-0.058 to 0.110	0.55						
Right bronchus intermedius	0.019	-0.077 to 0.115	0.70						
Lobar only	<ref>								
<b>Obstruction type of most proximal location</b>									
Endobronchial	<ref>								
Extrinsic	-0.025	-0.082 to 0.032	0.39						
Mixed	-0.008	-0.105 to 0.055	0.85						
<b>Explanatory variables</b>									
ΔBorg	-0.023	-0.024	<0.001				-0.021	-0.033 to -0.009	<0.001
<b>Ventilation type</b>									
Jet ventilation	0.015	-0.065 to 0.095	0.72						
Volume cycled	<ref>								
<b>Bronchoscopy type</b>									
Rigid and flexible	0.006	-0.084 to 0.096	0.89						
Flexible only	<ref>								
<b>Treatment modalities</b>									

Continued

Table 3 Continued

	Univariate			Multivariate predictive			Multivariate explanatory		
	Coefficient	95% CI	P values	Coefficient	95% CI	P values	Coefficient	95% CI	P values
Any laser	0.037	−0.028 to 0.102	0.26						
Electrocautery	0.047	−0.004 to 0.098	0.07						
Argon plasma	0.025	−0.024 to 0.074	0.33						
Cryorecanalisation	0.076	0.019 to 0.133	0.01						
Microdebrider	−0.015	−0.070 to 0.040	0.61						
Rigid 'coring'	0.068	−0.008 to 0.144	0.08						
Dilation	−0.064	−0.123 to −0.005	0.04						
Stent at first procedure	−0.031	−0.082 to 0.020	0.23						
Stent type placed									
Aero	0.003	−0.075 to 0.081	0.94						
Y-Stent	0.018	−0.064 to 0.100	0.66						
Technical success									
Complete or partial	0.003	−0.075 to 0.081	0.94						
Failed	<ref>								
Postprocedure treatment									
Surgery	−0.097	−0.220 to 0.026	0.13						
Chemotherapy	−0.002	−0.051 to 0.047	0.93						
Radiation therapy	0.01	−0.039 to 0.059	0.69						

\*Day-7 utility score is 7 days after the study entry bronchoscopy. If the patient had subsequent bronchoscopies, these were not included in this analysis.

†Patients could have one or more comorbidities, so each comorbidity is dichotomous. For therapeutic bronchoscopy indication(s), patients could have more than one indication for bronchoscopy, but one of them had to be for malignant central airway obstruction.

explanatory analysis, higher baseline Borg score, having fewer lung segments occluded and  $\Delta$ utility-day-7 were associated with a higher  $\Delta$ utility-long-term. In univariate explanatory analysis, 59% of the observed variability in  $\Delta$ utility-long-term was explained by the linear relationship between  $\Delta$ utility-long-term and  $\Delta$ utility-day-7 (ie, adjusted  $R^2=0.59$ ).

### Survival

Median survival was 179 days (95% CI 107 to 271). The factors associated with survival in the predictive Cox model (table 6) were the same as those associated with quality-adjusted survival. When we limited the explanatory model to the same covariates as used for quality-adjusted survival, the factors identified were again largely the same as with quality-adjusted survival. The one difference was that cardiovascular disease was associated with decreased survival but not associated with decreased quality-adjusted survival.

We then built extended Cox models to assess the impact of variables that vary over time on survival, such as lower respiratory tract infections, dyspnoea, HRQOL and whether or not a stent was in place (table 7). Taking into consideration these time-varying covariates, we found better baseline performance status as measured by Zubrod, higher HRQOL (utility) and receiving chemotherapy following therapeutic bronchoscopy were associated with improved survival. Conversely, lower respiratory tract infections were associated with increased mortality risk.

### DISCUSSION

Therapeutic bronchoscopy for malignant CAO is essentially a palliative intervention. While therapeutic bronchoscopy may extend life in some patients with malignant CAO, such as those on mechanical ventilation due to CAO, for the majority of patients the goal is relief of dyspnoea and improvement in HRQOL. In deciding whether therapeutic bronchoscopy is likely to benefit a given patient, it is therefore necessary to consider

the probability of technical success, the magnitude of the impact that technical success is likely to have on dyspnoea, whether or not that benefit is likely to be maintained over time and how that in turn will impact long-term HRQOL and quality-adjusted survival. The potential benefits in long-term HRQOL must then be weighed against the risks of intervention. To the best of our knowledge, this study is the first to quantify long-term quality-adjusted survival following therapeutic bronchoscopy for malignant CAO and to identify the factors associated with it. Median quality-adjusted survival was 109 QALDs (95% CI 74 to 201 QALDs). Factors associated with improved quality-adjusted survival included better baseline performance status, less dyspnoea at baseline, having a treatment-naïve tumour, endobronchial disease, shorter time from cancer diagnosis to intervention and receiving follow-up chemotherapy. Therapeutic bronchoscopy resulted in immediate improvements in dyspnoea and utility. Importantly, these improvements over baseline were maintained long-term such that HRQOL per day of life improved compared with prebronchoscopy levels.

Previous investigators have demonstrated improvements in dyspnoea and quality of life.<sup>1–14</sup> However, these prior studies cannot fully inform clinical decision making because the benefits of intervention must be weighed against the risks but the trade-offs involved have different units.<sup>3</sup> For example, how much risk does technical success warrant, when technical success is measured in relief of luminal narrowing and risk might be measured as pneumothorax or death? Dyspnoea is a more relevant patient-centred outcome, but how much risk of death does a clinically significant one unit change in Borg score warrant?

So benefit needs to be quantified in units that allow physicians to compare the benefits with the risks involved. This requires use of generic single-index measures of HRQOL such as the SF-6D that can be used to generate utilities (see the online supplement). The AQUIRE registry study of therapeutic bronchoscopy was the first to do this for short-term outcomes, reporting a mean baseline



Table 4 Factors associated with quality-adjusted survival time

	Univariate			Multivariate predictive			Explanatory		
	HR*	95% CI	P values	HR*	95% CI	P values	HR*	95% CI	P values
<b>Predictive variables</b>									
Age	0.998	0.98 to 1.02	0.87						
Male gender	0.73	0.46 to 1.16	0.18						
Zubrod 2–4 vs 0–1	3.64	2.26 to 5.87	<0.001	3.67	2.14 to 6.29	<0.001	5.07	2.83 to 9.1	<0.001
Urgent/emergent vs elective	1.57	0.92 to 2.66	0.1						
Time from diagnosis to procedure (weeks)	1	1.00 to 1.00	0.18				0.998	0.996 to 0.9997	0.02
Baseline Borg	1.16	1.07 to 1.25	<0.001	1.13	1.03 to 1.24	0.008	1.12	1.02 to 1.23	0.02
Baseline utility	2.25	0.43 to 11.73	0.34						
<b>Comorbidities†</b>									
COPD	0.79	0.4 to 1.54	0.49						
Cardiovascular	1.57	0.95 to 2.6	0.08				1.97	1.04 to 3.74	0.038
Diabetes	0.84	0.48 to 1.46	0.54						
Second primary	1.29	0.64 to 2.6	0.48						
<b>Cancer type</b>									
Lung	0.93	0.59 to 1.46	0.75						
Other malignancies	<ref>								
<b>Initial treatment type</b>									
Surgery	1.43	0.75 to 2.72	0.28	2.13	1.03 to 4.4	0.04	4.74	1.98 to 11.36	<0.001
Chemotherapy	2.81	1.44 to 5.46	0.002	3.42	1.6 to 7.27	0.004	3.87	1.77 to 8.45	0.001
Radiation therapy	2.34	1.06 to 5.2	0.04	2.21	0.92 to 5.3	0.07	2.1	0.87 to 5.08	0.1
No treatment	<ref>			<ref>			<ref>		
Any prior therapeutic bronchoscopy	0.3	0.1 to 0.97	0.04						
<b>Indication(s) for therapeutic bronchoscopy†</b>									
Tracheoesophageal fistula	1.27	0.4 to 4.04	0.69						
Haemoptysis	0.61	0.34 to 1.11	0.11						
Number of bronchopulmonary segments obstructed	1.06	1.01 to 1.11	0.02						
<b>Location of most proximal obstruction</b>									
Trachea	1.6	0.76 to 3.36	0.22						
Bilateral mainstem	2.1	0.77 to 5.72	0.15						
Right mainstem	1.01	0.48 to 2.11	0.98						
Left mainstem	0.74	0.33 to 1.68	0.47						
Right bronchus intermedius	0.96	0.4 to 2.31	0.92						
Lobar only	<ref>								
<b>Obstruction type of most proximal location</b>									
Endobronchial	<ref>			<ref>			<ref>		
Extrinsic	2.15	1.29 to 3.57	0.003	2.8	1.6 to 4.88	<0.001	2.88	1.61 to 5.12	<0.001
Mixed	3.8	1.91 to 7.59	<0.001	2.13	0.97 to 4.68	0.06	1.66	0.71 to 3.86	0.24
<b>Explanatory variables</b>									
<b>Ventilation type</b>									
Jet ventilation	1.86	0.75 to 4.6	0.18						
Volume cycled	0.64	0.28 to 1.48	0.3						
<b>Bronchoscopy type</b>									
Rigid and flexible	1.23	0.53 to 2.83	0.63						
Flexible only	<ref>								
<b>Treatment modalities</b>									
Any laser	0.48	0.24 to 0.97	0.04						

Continued

Table 4 Continued

	Univariate			Multivariate predictive			Explanatory		
	HR*	95% CI	P values	HR*	95% CI	P values	HR*	95% CI	P values
Electrocautery	0.62	0.37 to 1.04	0.07						
Argon plasma	0.9	0.57 to 1.42	0.65						
Cryorecanalisation	0.69	0.38 to 1.25	0.22						
Microdebrider	0.72	0.42 to 1.23	0.22						
Rigid 'coring'	0.77	0.37 to 1.6	0.48						
Dilation	1.57	0.91 to 2.7	0.1				2.21	1.16 to 4.19	0.02
Stent at first procedure	2.27	1.44 to 3.59	<0.001						
Stent type placed									
Aero	1.23	0.52 to 2.95	0.64						
Y-Stent	0.74	0.3 to 1.86	0.52						
Technical success									
Complete or partial	0.64	0.32 to 1.29	0.21						
Failed	<ref>								
Postprocedure treatment									
Chemotherapy	0.88	0.56 to 1.38	0.58				0.44	0.26 to 0.74	0.002
Radiation therapy	0.52	0.33 to 0.83	0.01						

\*Higher HR represents an increased risk for shorter quality-adjusted survival.

†Patients could have one or more comorbidities, so each comorbidity is dichotomous. For therapeutic bronchoscopy indication(s), patients could have more than one indication for bronchoscopy, but one of them had to be for malignant central airway obstruction.

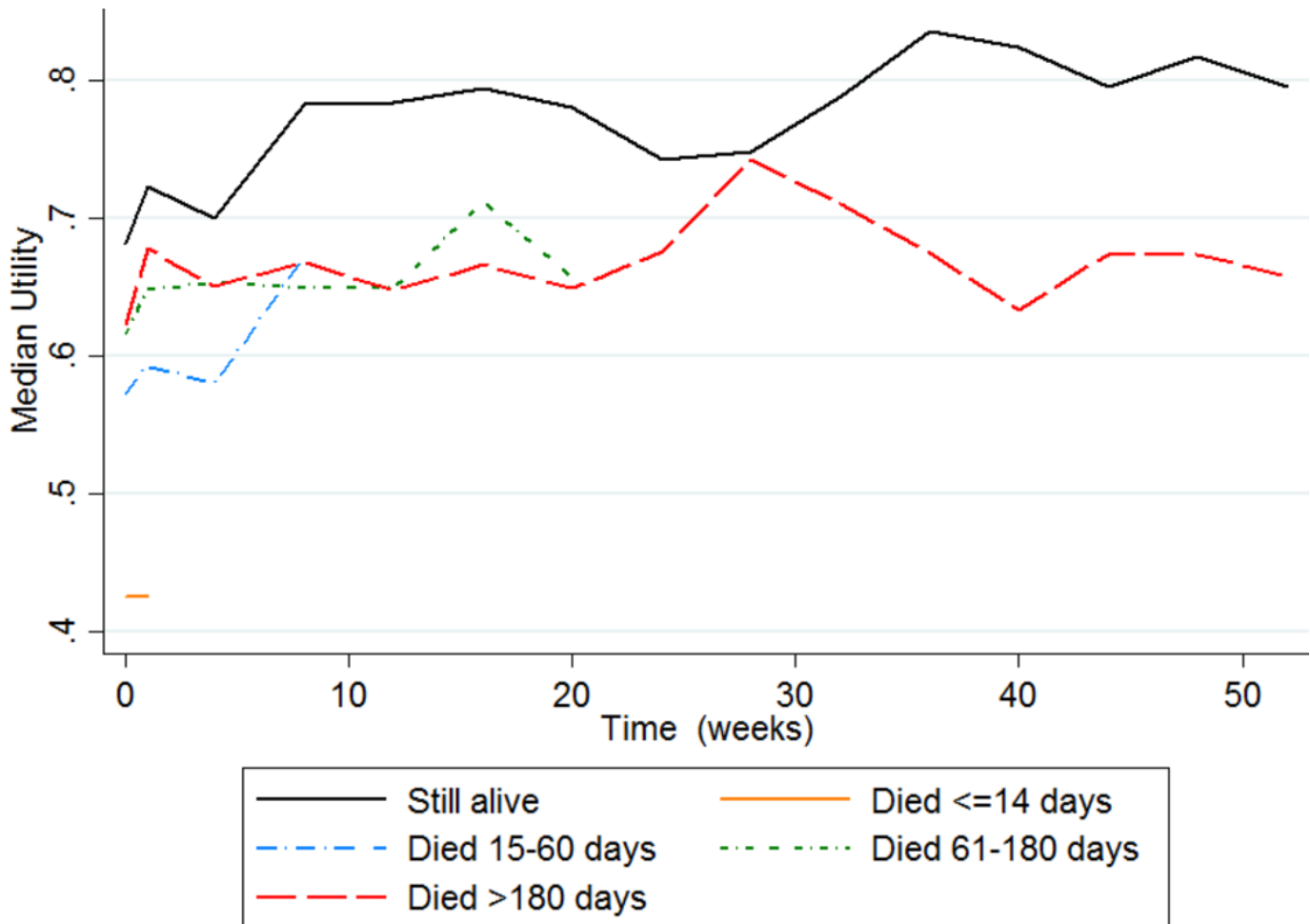


Figure 2 Changes in median utility over time by survivor group.

**Table 5** Factors associated with mean benefit per day of life measured in utility

	Univariate			Multivariate predictive			Multivariate explanatory		
	Coefficient	95% CI	P values	Coefficient	95% CI	P values	Coefficient	95% CI	P values
<b>Predictive variables</b>									
Age	0	−0.002 to 0.002	0.94						
Male gender	−0.008	−0.053 to 0.037	0.71						
Zubrod 2–4 vs 0–1	0.009	−0.034 to 0.052	0.69						
Baseline utility	−0.478	−0.596 to −0.360	<0.001*						
Baseline Borg	0.019	0.011 to 0.027	<0.001	0.022	0.014 to 0.030	<0.001	0.012	0.007 to 0.018	<0.001
Urgent/emergent vs elective	0.026	−0.027 to 0.079	0.33						
Time from diagnosis to procedure (weeks)	−0.00006	−0.00017 to 0.00005	0.77						
<b>Comorbidities</b>									
COPD	0.009	−0.054 to 0.073	0.77						
Cardiovascular	0.002	−0.048 to 0.053	0.92						
Diabetes	0.027	−0.024 to 0.079	0.29						
Second primary solid tumour	−0.016	−0.087 to 0.054	0.65						
<b>Cancer type</b>									
Lung	0.028	−0.016 to 0.072	0.21						
Other malignancies	<ref>								
<b>Initial treatment type</b>									
Surgery	−0.016	−0.069 to 0.038	0.57						
Chemotherapy	−0.019	−0.077 to 0.039	0.52						
Radiation therapy	0.015	−0.057 to 0.086	0.68						
No treatment	<ref>								
Any prior therapeutic bronchoscopy	−0.087	−0.16 to −0.007	0.03						
<b>Indication(s) for therapeutic bronchoscopy*</b>									
Tracheoesophageal fistula	−0.064	−0.176 to 0.048	0.26						
Haemoptysis	0.009	−0.045 to 0.063	0.73						
Number of bronchopulmonary segments obstructed	−0.003	−0.007 to 0.001	0.20	−0.006	−0.010 to −0.002	0.006	−0.003	−0.006 to −0.0002	0.036
<b>Location of most proximal obstruction</b>									
Trachea	−0.027	−0.010 to 0.045	0.46						
Bilateral mainstem	−0.047	−0.146 to 0.053	0.36						
Right mainstem	0.032	−0.038 to 0.101	0.37						
Left mainstem	−0.023	−0.099 to 0.053	0.55						
Right bronchus intermedius	0.026	−0.060 to 0.094	0.55						
Lobar only	<ref>								
<b>Obstruction type of most proximal location</b>									
Endobronchial	<ref>								
Extrinsic	−0.043	−0.093 to 0.007	0.09						
Mixed	−0.031	−0.102 to 0.040	0.39						
<b>Explanatory variables</b>									
ΔBorg at day-7	−0.023	−0.035 to −0.011	<0.001						
ΔUtility at day-7	0.693	0.581 to 0.805	<0.001				0.612	0.498 to 0.725	<0.001
<b>Ventilation type</b>									
Jet ventilation	−0.005	−0.078 to 0.069	0.90						
Volume cycled	<ref>								
<b>Bronchoscopy type</b>									
Rigid and flexible	−0.019	−0.100 to 0.062	0.65						
Flexible only	<ref>								

Continued

Table 5 Continued

	Univariate			Multivariate predictive			Multivariate explanatory		
	Coefficient	95% CI	P values	Coefficient	95% CI	P values	Coefficient	95% CI	P values
Treatment modalities									
Any laser	0.01	-0.049 to 0.068	0.75						
Electrocautery	0.047	0.001 to 0.094	0.04						
Argon plasma	0.007	-0.038 to 0.052	0.76						
Cryorecanalisation	0.081	0.030 to 0.133	0.002						
Microdebrider	-0.004	-0.1	0.88						
Rigid 'coring'	0.038	-0.032 to 0.108	0.29						
Dilation	-0.042	-0.097 to 0.012	0.13						
Stent at first procedure	-0.035	-0.081 to 0.011	0.14						
Technical success									
Complete or partial	0.003	-0.068 to 0.073	0.94						
Failed	<ref>								
Postprocedure treatment									
Surgery	-0.058	-0.170 to 0.054	0.31						
Chemotherapy	0.004	-0.041 to 0.048	0.87						
Radiation therapy	0.004	-0.040 to 0.048	0.87						

\*Plot of residuals vs fitted values and White's tests indicate significant heteroscedasticity; values reported but not used in multivariate model.

HRQOL of 0.65 utilities, a  $\Delta$ utility-day-30 of +0.023 utilities and a  $\Delta$ Borg-day-30 of -0.9.<sup>3</sup> In AQUIRE, for every one unit increase in  $\Delta$ Borg-day-30,  $\Delta$ utility-day-30 changed by -0.020 utilities (ie, more dyspnoea, lower HRQOL). In this study, baseline HRQOL was 0.618 utilities,  $\Delta$ utility-day-7 was +0.047 utilities,  $\Delta$ Borg-day-7 was -1.8 and for every one unit increase in  $\Delta$ Borg-day-7,  $\Delta$ utility-day-7 changed by -0.021 utilities. So in terms of the short-term impact of therapeutic bronchoscopy on dyspnoea and HRQOL, our findings are similar to AQUIRE.<sup>3</sup> The present findings are also consistent with those in the literature, which demonstrate that for non-small cell lung cancer, utilities for health states for cancer-related outcome range from 0.70 (responding to therapy) to 0.47 (progressive disease) to 0.33 (end of life).<sup>28</sup>

The effect size observed in this study for short-term outcomes was somewhat greater for change in utility and dyspnoea than in AQUIRE, but the relationship between  $\Delta$ Borg and  $\Delta$ utility was similar. Part of the difference between studies may be due to the use of day-7 outcomes versus day-30 outcomes. We chose day-7 outcomes as a measure of the immediate impact of therapeutic bronchoscopy rather than the previously published day-30 based on what we learnt from AQUIRE. In AQUIRE, we found that many patients received additional treatments (eg, chemotherapy) within 30 days, which confounds the assessment of the impact of bronchoscopy on utility, since changes could be due to factors other than bronchoscopy. So the increased effect size observed in this study for relatively short-term outcomes is likely a combination of differences in timing of measurement, centre-level variability and patient selection.

However, while knowledge of the determinants of short-term outcomes following therapeutic bronchoscopy for malignant central airway obstruction is useful, it is not sufficient. We need to be able to quantify long-term benefits as well. One of the key questions unanswered by AQUIRE was whether short-term improvements in dyspnoea and utility are maintained over time and how much do they impact quality-adjusted survival. This study adds to the existing body of knowledge by quantifying the long-term quality-adjusted survival of patients undergoing therapeutic bronchoscopy. Our findings suggest that long-term HRQOL per day of life following therapeutic bronchoscopy was

significantly better than the prebronchoscopy baseline ( $\Delta$ utility-long-term+0.036 utilities per day of life).

This change in long-term HRQOL represents the aggregate of a multimodality approach, not just bronchoscopy (see online supplement e-table 3). However, much of the observed improvement is probably due to a sustained reduction in dyspnoea. This reduction in dyspnoea is initially achieved with bronchoscopy and is subsequently maintained over time. This is supported by our finding that the short-term impact of therapeutic bronchoscopy on dyspnoea ( $\Delta$ Borg-day-7) was strongly associated with short-term HRQOL changes ( $\Delta$ utility-day-7). Short-term HRQOL changes were also strongly associated with long-term changes in HRQOL as measured by  $\Delta$ utility-long-term (table 5, adjusted  $R^2=0.59$  for  $\Delta$ utility-day-7 impact on  $\Delta$ utility-long-term). Since changes in utility from prebronchoscopy to 7 days postbronchoscopy are most likely due to the effects of therapeutic bronchoscopy rather than other treatments (eg, chemotherapy), the finding that  $\Delta$ utility-day-7 explains 59% of the variance in long-term HRQOL suggests that the short-term benefits of therapeutic bronchoscopy are maintained over time and help drive improvements in long-term HRQOL.

Comparing therapeutic bronchoscopy as part of a multimodality approach with radiation therapy (RT) alone for malignant CAO is difficult because improvements in RT dosing and delivery limit the value of historical comparisons. In addition, there is very little data on RT for malignant CAO. However, historical data from when therapeutic bronchoscopy was not available can provide some useful insights provided we keep these limitations in mind.<sup>4</sup> A study from the Mayo Clinic found that laser resection for malignant CAO improved survival (40% mortality at 7 months and 72% at 1 year) as compared with historical controls that received radiation (76% mortality at 4 months and 100% mortality by 7 months).<sup>29</sup> The Cleveland Clinic published data on Nd:YAG laser/RT versus historical controls receiving RT and found better survival with bronchoscopy when the airway obstruction was emergent (267 vs 150 days,  $p=0.04$ ).<sup>30</sup> In the same series, taking both emergent and non-emergent cases, there was no survival difference (YAG 304 days vs RT 253 days,  $p=0.17$ ). A study of mechanically ventilated patients with

**Table 6** Factors associated with time to death, predictive Cox model

	Univariate			Multivariate predictive		
	HR	95% CI	P values	HR	95% CI	P values
<b>Predictive variables</b>						
Age	1.001	0.98 to 1.02	0.9			
Male gender	0.78	0.50 to 1.23	0.28			
Zubrod 2–4 vs 0–1	3.59	2.22 to 5.80	<0.001	3.71	2.14 to 6.45	<0.001
Urgent/emergent vs elective	1.51	0.89 to 2.56	0.13			
Time from diagnosis to procedure (weeks)	1	1.00 to 1.00	0.18			
Baseline Borg	1.15	1.07 to 1.25	<0.001	1.11	1.01 to 1.21	0.03
Baseline utility	2.31	0.45 to 11.83	0.32			
<b>Comorbidities</b>						
COPD	0.74	0.38 to 1.44	0.38			
Cardiovascular	1.62	0.98 to 2.67	0.06			
Diabetes	0.85	0.49 to 1.45	0.54			
Second primary	1.57	0.83 to 2.99	0.17			
<b>Cancer type</b>						
Lung	0.93	0.59 to 1.46	0.75			
Other malignancies	<ref>					
<b>Initial treatment type</b>						
Surgery	1.39	0.74 to 2.61	0.3	1.99	0.99 to 4.02	0.05
Chemotherapy	2.6	1.35 to 5.00	0.004	2.93	1.41 to 6.09	0.004
Radiation therapy	2.44	1.13 to 5.24	0.02	2.02	0.86 to 4.79	0.11
No treatment	<ref>			<ref>		
Any prior therapeutic bronchoscopy	0.38	0.14 to 1.04	0.06			
<b>Indication(s) for therapeutic bronchoscopy</b>						
Tracheoesophageal fistula	1.19	0.37 to 3.80	0.77			
Haemoptysis	0.62	0.35 to 1.11	0.11			
Number of bronchopulmonary segments obstructed	1.05	1.01 to 1.10	0.03			
<b>Location of most proximal obstruction</b>						
Trachea	1.58	0.75 to 3.32	0.23			
Bilateral mainstem	2.11	0.77 to 5.77	0.15			
Right mainstem	1.11	0.54 to 2.31	0.78			
Left mainstem	0.78	0.34 to 1.78	0.56			
Right bronchus intermedius	1.19	0.50 to 2.80	0.7			
Lobar only	<ref>					
<b>Obstruction type of most proximal location</b>						
Endobronchial	<ref>			<ref>		
Extrinsic	2.01	1.21 to 3.32	0.01	2.66	1.53 to 4.62	0.001
Mixed	3.31	1.68 to 6.54	0.001	1.82	0.82 to 4.03	0.139
<b>Explanatory variables</b>						
<b>Ventilation type</b>						
Jet ventilation	1.59	0.69 to 3.66	0.27			
Volume cycled	0.61	0.27 to 1.42	0.25			
<b>Bronchoscopy type</b>						
Rigid and flexible	1.23	0.53 to 2.83	0.63			
Flexible only	<ref>					

Continued

Table 6 Continued

	Univariate			Multivariate predictive		
	HR	95% CI	P values	HR	95% CI	P values
<b>Treatment modalities</b>						
Any laser	0.48	0.24 to 0.95	0.04			
Electrocautery	0.67	0.40 to 1.10	0.11			
Argon plasma	0.85	0.54 to 1.33	0.48			
Cryorecanalisation	0.73	0.41 to 1.31	0.29			
Microdebrider	0.78	0.46 to 1.32	0.35			
Rigid 'coring'	0.79	0.38 to 1.64	0.52			
Dilation	1.42	0.83 to 2.43	0.2			
<b>Stent type placed</b>						
Aero	1.17	0.50 to 2.73	0.71			
Y-Stent	0.8	0.33 to 1.94	0.63			
<b>Technical success</b>						
Complete or partial	0.69	0.34 to 1.38	0.3			
Failed	<ref>					
<b>Postprocedure treatment</b>						
Chemotherapy	0.54	0.34 to 0.84	0.01			
Radiation therapy	0.86	0.55 to 1.35	0.52			
<b>Time-varying covariates</b>						
Presence of stent	2.47	1.56 to 3.91	<0.001			
Utility	0.002	0.0003 to 0.011	<0.001			
Borg score	1.22	1.14 to 1.31	<0.001			
Lower respiratory tract infection	2.35	0.72 to 7.63	<0.001			

Utility range is from 0 to 1. So for a 0.01 unit increase in utility as a time-varying covariate, the HR is  $0.002^{0.01}=0.94$ . So for each 0.01 increase in utility, the hazard rate of death decreases by 6%. Note that this is exponential, so for a 0.1 increase in utility, the hazard rate of death does not decrease by 60%. Rather it is  $0.002^{0.1}=0.54$ . So an increase in utility of 0.1 is associated with a 46% decrease in the hazard rate of death.

malignant central airway obstruction found that those with successful reopening of the airway did better and received additional chemo-RT after successful extubation.<sup>31</sup> Unfortunately, none of these studies measured quality-adjusted survival.

We believe that quantifying the impact of therapeutic bronchoscopy on dyspnoea and quality-adjusted survival can help inform clinical decision making. We found that the impact of bronchoscopic intervention is maximal early on (ie,  $\Delta$ utility-day-7+0.047 utilities), but as the disease progresses and side effects set in HRQOL is impacted ( $\Delta$ utility-long-term+0.036 utilities per day of life). A conservative assumption regarding therapeutic bronchoscopy is that it does not extend duration of life at all, it does not prevent any postobstructive pneumonias, and its only benefit is that it improves HRQOL by alleviating dyspnoea related to CAO obstruction. The initial  $\Delta$ utility-day-7 provides an upper limit estimate of the impact of therapeutic bronchoscopy on HRQOL based on these assumptions. Over the long-term, this estimate may be too high—time and disease will mitigate the beneficial effects, so  $\Delta$ utility-long-term provides a more conservative assessment of benefit. Since this is not a randomised controlled trial, we cannot provide a more precise assessment of the impact of therapeutic bronchoscopy as compared with the alternative of not doing bronchoscopy. While such a randomised controlled trial would be informative, it would not be ethical, and as such we believe using  $\Delta$ utility-long-term provides a practical if not perfect estimate of the effect of therapeutic bronchoscopy on HRQOL. Given these limitations, what we can say with confidence is that HRQOL per day of life postbronchoscopy is

on average better than it was prebronchoscopy and this effect is maintained over time.

Because physicians do not often deal with utility, it can be difficult for clinicians to interpret how large an effect size this represents. So for clinical practice it can be helpful to put utility numbers into clinical context in order to calibrate judgement. So how much does a change of +0.036 utilities per day of life represent? First, let us remember that mean baseline utility was 0.618 utilities, so this represents a 5.8% improvement. Since we are evaluating quality-adjusted survival, this improvement in HRQOL is equivalent to living 5.8% longer if HRQOL were to remain at baseline levels.

Another way to gain clinical context is to compare this effect with the effect of more common interventions in similar populations. However, comparing the impact of interventions between very different populations using QALYs is not always valid (see online supplement).<sup>32–35</sup> Care must be taken when choosing a comparator population and intervention. Given these limitations, the most analogous population for which there is data is probably patients with malignant pleural effusions (MPE).<sup>15</sup> Both populations have metastatic cancer, both have similar life expectancies and in both cases the palliative intervention is aimed at dyspnoea relief. Unlike malignant CAO, MPE is a very common problem for many pulmonologists, so a comparison can provide context to the utility measures being reported. In a prospective observational study of 266 patients undergoing indwelling pleural catheter (IPC) placement for MPE, HRQOL at 1 month post-IPC increased compared with baseline by +0.023 utilities.<sup>15</sup>



**Table 7** Factors associated with time to death, multivariate explanatory extended Cox models

	Cox model			Extended Cox model		
	HR	95% CI	P values	HR	95% CI	P values
<b>Predictive variables</b>						
Zubrod 2–4 vs 0–1	4.4	2.55 to 7.60	<0.001	3.02	1.83 to 5.00	<0.001
Time from diagnosis to procedure (weeks)	0.998	0.996 to 0.9996	0.02			
Comorbidities: cardiovascular	1.76	1.00 to 3.08	0.05			
<b>Initial treatment type</b>						
Surgery	3.54	1.60 to 7.81	0.002			
Chemotherapy	2.98	1.47 to 6.05	0.002			
Radiation therapy	2.62	1.15 to 5.99	0.02			
No treatment	<ref>					
<b>Obstruction type of most proximal location</b>						
Endobronchial	<ref>					
Extrinsic	2.63	1.54 to 4.50	<0.001			
Mixed	2.35	1.13 to 4.86	0.02			
<b>Explanatory variables</b>						
<b>Postprocedure treatment</b>						
Chemotherapy	0.42	0.26 to 0.69	0.001	0.51	0.32 to 0.81	0.004
<b>Time-varying covariates</b>						
Utility				0.003	0.001 to 0.02	<0.001
Lower respiratory tract infection				3.79	1.13 to 12.71	0.03

So as a rough approximation, the mean change in HRQOL immediately following therapeutic bronchoscopy at day-7 is double that seen with drainage of a MPE (+0.047 vs +0.023 utiles, respectively). Over the long-term, the impact of bronchoscopy is roughly one-and-a-half times as much as the improvement seen with an IPC.

This improvement in HRQOL must be weighed against the risks. While there were no fatal procedural complications in this study, the overall rate of fatal procedural complications reported in AQUIRE was 0.5%.<sup>27</sup> The overall risk-benefit ratio of therapeutic bronchoscopy is very favourable if we use 0.5% as our estimate of fatal procedural complications and consider  $\Delta$ utility-long-term as roughly a 5.8% improvement over baseline.

Although these findings are useful, it is important to recognise the limitations of the data. This was a single-centre prospective observational study. The generalisability of the results to other centres may be limited. There is significant heterogeneity between centres in terms of methods of therapeutic bronchoscopy, complication rates and 30-day mortality.<sup>3,27</sup> The impact of therapeutic bronchoscopy observed in this study may vary from that of other centres depending on patient referral patterns, patient selection and bronchoscopic techniques. In addition, as with any long-term longitudinal study, imputation for missing data can be a problem. We prespecified the LOCF method based on prior studies,<sup>15</sup> but the LOCF methodology can be prone to bias under certain conditions (see online supplement).<sup>36,37</sup> However, because we sampled so frequently (ie, monthly) the inpatient variation between months in utility was low, such that whether we used an LOCF or a carry-backwards imputation method, this did not change the results. Note that the limitations of imputation in this study only apply to the long-term outcomes, not the day-7 outcomes.

In conclusion, this study supports and extends the findings of the AQUIRE group. The data suggest that when baseline dyspnoea is more severe there is greater potential for therapeutic bronchoscopy to have a meaningful impact on utility.<sup>3</sup> The impact of bronchoscopic interventions, especially when done as part of multimodality treatment, are such that the improvements in dyspnoea and utility are likely to be sustained for most patients. While immediate and long-term complications are significant, given the observed rates in this trial and other large series,<sup>1–14</sup> the risk-benefit ratio can be considered favourable, provided the malignant CAO is causing significant dyspnoea that is contributing to the patient's poor HRQOL. Future studies using more formal decision analysis techniques will be needed to further clarify the decision thresholds and trade-offs involved. The magnitude of the change in HRQOL following therapeutic bronchoscopy is roughly equivalent to a 5.8% improvement in quality-adjusted survival.

**Acknowledgements** The authors would like to thank Dr Xiudong Lei, PhD, biostatistics department for her help with power calculations and design and Dr Liang Li for his help with imputation analysis.

**Contributors** DEO was the principal investigator (PI) for this study and was involved in project oversight, organisation, data collection and auditing, statistical analysis and manuscript writing. PO did the statistical analysis and was involved in manuscript writing. HBG, LD, CAJ, GAE and RFC were involved in data collection and auditing, and manuscript writing. LN contributed to data collection, auditing and review.

**Funding** This study was funded by NIH/NCI biostatistic core (P30CA016672), biostatistics core, at the University of Texas, MD Anderson Cancer Center and Institutional Research Grant from MD Anderson Cancer Center.

**Competing interests** None declared.

**Patient consent** Obtained.

**Ethics approval** Institutional review board approval was obtained from The University of Texas MD Anderson IRB Committee 4.

**Provenance and peer review** Not commissioned; externally peer reviewed.

## REFERENCES

- Ernst A, Simoff M, Ost D, *et al.* Prospective risk-adjusted morbidity and mortality outcome analysis after therapeutic bronchoscopic procedures: results of a multi-institutional outcomes database. *Chest* 2008;134:514–9.
- Casal RF, Iribarren J, Eapen G, *et al.* Safety and effectiveness of microdebrider bronchoscopy for the management of central airway obstruction. *Respirology* 2013;18:1011–5.
- Ost DE, Ernst A, Grosu HB, *et al.* Therapeutic bronchoscopy for malignant central airway obstruction: success rates and impact on dyspnea and quality of life. *Chest* 2015;147:1282–98.
- Ernst A, Feller-Kopman D, Becker HD, *et al.* Central airway obstruction. *Am J Respir Crit Care Med* 2004;169:1278–97.
- Seijo LM, Sterman DH. Interventional pulmonology. *N Engl J Med* 2001;344:740–9.
- Husain SA, Finch D, Ahmed M, *et al.* Long-term follow-up of ultraflex metallic stents in benign and malignant central airway obstruction. *Ann Thorac Surg* 2007;83:1251–6.
- Razi SS, Lebovics RS, Schwartz G, *et al.* Timely airway stenting improves survival in patients with malignant central airway obstruction. *Ann Thorac Surg* 2010;90:1088–93.
- Oviatt PL, Stather DR, Michaud G, *et al.* Exercise capacity, lung function, and quality of life after interventional bronchoscopy. *J Thorac Oncol* 2011;6:38–42.
- Furukawa K, Ishida J, Yamaguchi G, *et al.* The role of airway stent placement in the management of tracheobronchial stenosis caused by inoperable advanced lung cancer. *Surg Today* 2010;40:315–20.
- Amjadi K, Voduc N, Cruysberghs Y, *et al.* Impact of interventional bronchoscopy on quality of life in malignant airway obstruction. *Respiration* 2008;76:421–8.
- Bolliger CT, Breitenbuecher A, Brutsche M, *et al.* Use of studded Polyflex stents in patients with neoplastic obstructions of the central airways. *Respiration* 2004;71:83–7.
- Bolliger CT, Sutudja TG, Strausz J, *et al.* Therapeutic bronchoscopy with immediate effect: laser, electrocautery, argon plasma coagulation and stents. *Eur Respir J* 2006;27:1258–71.
- Bolliger CT, Mathur PN, Beamis JF, *et al.* ERS/ATS statement on interventional pulmonology. European Respiratory Society/American Thoracic Society. *Eur Respir J* 2002;19:356–73.
- Wood DE, Liu YH, Vallières E, *et al.* Airway stenting for malignant and benign tracheobronchial stenosis. *Ann Thorac Surg* 2003;76:167–74.
- Ost DE, Jimenez CA, Lei X, *et al.* Quality-adjusted survival following treatment of malignant pleural effusions with indwelling pleural catheters. *Chest* 2014;145:1347–56.
- Deslée G, Mal H, Dutau H, *et al.* Lung volume reduction coil treatment vs usual care in patients with severe emphysema: The REVOLENS Randomized Clinical Trial. *JAMA* 2016;315:175–84.
- Rawlins MD, Culyer AJ. National institute for clinical excellence and its value judgments. *BMJ* 2004;329:224–7.
- Weinstein MC, Siegel JE, Gold MR, *et al.* Recommendations of the panel on cost-effectiveness in health and medicine. *JAMA* 1996;276:1253–8.
- Siegel JE, Torrance GW, Russell LB, *et al.* Guidelines for pharmacoeconomic studies. recommendations from the panel on cost effectiveness in health and medicine. panel on cost effectiveness in health and medicine. *Pharmacoeconomics* 1997;11:159–68.
- Siegel JE, Weinstein MC, Russell LB, *et al.* Recommendations for reporting cost-effectiveness analyses. panel on cost-effectiveness in health and medicine. *JAMA* 1996;276:1339–41.
- Atkins D, DiGiuseppe CG. Broadening the evidence base for evidence-based guidelines. A research agenda based on the work of the U.S. Preventive Services Task Force. *Am J Prev Med* 1998;14:335–44.
- Eapen GA, Shah AM, Lei X, *et al.* Complications, consequences, and practice patterns of endobronchial ultrasound-guided transbronchial needle aspiration: Results of the AQUIRE registry. *Chest* 2013;143:1044–53.
- Yarnus LB, Akulian J, Lechtzin N, *et al.* Comparison of 21-gauge and 22-gauge aspiration needle in endobronchial ultrasound-guided transbronchial needle aspiration: results of the american college of chest physicians quality improvement registry, education, and evaluation registry. *Chest* 2013;143:1036–43.
- Ost DE, Ernst A, Lei X, *et al.* Diagnostic yield of endobronchial ultrasound-guided transbronchial needle aspiration: results of the AQUIRE Bronchoscopy Registry. *Chest* 2011;140:1557–66.
- Harris PA, Taylor R, Thielke R, *et al.* Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
- Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002;21:271–92.
- Ost DE, Ernst A, Grosu HB, *et al.* Complications following therapeutic bronchoscopy for malignant central airway obstruction: results of the aquire registry. *Chest* 2015;148:450–71.
- Nafees B, Stafford M, Gavriel S, *et al.* Health state utilities for non small cell lung cancer. *Health Qual Life Outcomes* 2008;6:84.
- Brutinel WM, Cortese DA, McDougall JC, *et al.* A two-year experience with the neodymium-YAG laser in endobronchial obstruction. *Chest* 1987;91:159–65.
- Desai SJ, Mehta AC, VanderBrug Medendorp S, *et al.* Survival experience following Nd:YAG laser photoresection for primary bronchogenic carcinoma. *Chest* 1988;94:939–44.
- Stanopoulos IT, Beamis JF, Martinez FJ, *et al.* Laser bronchoscopy in respiratory failure from malignant airway obstruction. *Crit Care Med* 1993;21:386–91.
- Carr AJ, Higginson IJ. Are quality of life measures patient centred? *BMJ* 2001;322:1357–60.
- Dorman S, Jolley C, Abernethy A, *et al.* Researching breathlessness in palliative care: consensus statement of the national cancer research institute palliative care breathlessness subgroup. *Palliat Med* 2009;23:213–27.
- Higginson IJ, Carr AJ. Measuring quality of life: Using quality of life measures in the clinical setting. *BMJ* 2001;322:1297–300.
- Paci E, Miccinesi G, Toscani F, *et al.* Quality of life assessment and outcome of palliative care. *J Pain Symptom Manage* 2001;21:179–88.
- Salim A, Mackinnon A, Christensen H, *et al.* Comparison of data analysis strategies for intent-to-treat analysis in pre-test-post-test designs with substantial dropout rates. *Psychiatry Res* 2008;160:335–45.
- Molnar FJ, Hutton B, Fergusson D. Does analysis using "last observation carried forward" introduce bias in dementia research? *CMAJ* 2008;179:751–3.