



Cohort study investigating evolution and factors associated with dyspnoea after anatomic lung resection

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Background: Dyspnoea is common following surgical resection for non-small cell lung cancer (NSCLC). The effects range from reduced quality of life to impact on adjuvant therapy outcomes. Currently, dyspnoea beyond the immediate postoperative phase and risk factors are not well characterised. We hope to assess the evolution of patient-reported dyspnoea after anatomic lung resection and associated factors.

Methods: Single-centre cohort study with analysis on data collected longitudinally of 131 patients undergoing anatomic lung resections for NSCLC between September 2014 and December 2018. The European Organization for Research and Treatment Lung Cancer-specific Quality of Life Questionnaire Dyspnoea Scale was used to measure dyspnoea before and after surgery. Multivariable regression analysis was used to identify factors associated with clinically meaningful perioperative changes in dyspnoea at 6–12 months.

Results: Mean Dyspnoea Scale scores preoperatively and 6–12 months after resection were 12.6 (standard deviation 17.4) and 17.9 (standard deviation 20.5), respectively. Of all patients 31% experienced a clinically meaningful increase in dyspnoea, defined as >10 points between Dyspnoea Scale scores preoperatively and at 6–12 months. Comparatively, 71% of patients without preoperative symptoms of dyspnoea developed a clinically meaningful increase of dyspnoea postoperatively. After adjusting the analysis for baseline factors and preoperative Dyspnoea Scale score, female sex remained the only patient factor associated with increased postoperative dyspnoea at 6–12 months after surgery ($P=0.046$). A total of 34% of patients reported increased dyspnoea after lobectomies and 9% after segmentectomies ($P=0.014$). Segmentectomy (as opposed to larger resections) was the only surgical factor associated with lower risk of increased dyspnoea ($P=0.057$).

Conclusions: A clinically meaningful increase in dyspnoea is frequent after lung resection. Postoperative evolution of dyspnoea is non-predictable using objective baseline factors highlighting the importance of patient reported symptoms and involvement in clinical consultation.

Keywords: Non-small cell lung cancer (NSCLC); lung resection; quality of life (QOL); shortness of breath; post-operative

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Introduction

Background

Curative surgery for early-stage non-small cell lung cancer (NSCLC) is leading to a growing population of lung cancer survivors, requiring clinicians to consider the late effects of lung resection. Dyspnoea is common, occurring in up to 60% of patients postoperatively, of which up to 65% had no dyspnoea preoperatively (1). The physical and psychological changes that accompany dyspnoea can affect quality of life (QOL) and outcomes for treatment adjuvant therapies (2,3).

Rationale and knowledge gap

To date, the literature on anatomical lung resection focuses on the stratification of patients based on pulmonary function and oncological status, to allow selection for surgery based on risk of mortality (4). In clinical practice however, patients attending pre-operative counselling are also concerned about the short-term and long-term side effects of surgery. Understanding peri-operative evolution of patient-reported dyspnoea is critical to foster shared decision making. However, predicting the incidence of

dyspnoea with objective respiratory measures can yield inaccurate results. In addition, the literature does not characterise late post-operative dyspnoea well (5).

Investigation of factors associated with late post-operative dyspnoea is needed to define patient risk. Identification of high-risk patients could subsequently ensure better uptake of pulmonary rehabilitation programmes for suitable candidates. Pre-operative chest physiotherapy for chronic obstructive pulmonary disease (COPD) patients has been trialled, demonstrating encouraging results (6). Further research should examine the extension of such programmes to high-risk dyspnoea patient groups undergoing lung resection to determine the potential for improved clinical outcomes.

Objective

The objective of this study is to investigate how patient reported dyspnoea evolves following lung resection and to explore associated factors. We present this article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-835/rc>).

Methods

Study design

This study was a prospective cohort study using non-consecutive cases.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Formal ethical approval was not required, and this study was classified as a service evaluation so did not require an NHS Research and Ethics Committee review.

Data collection, settings and time frames

Longitudinal data collection was performed on patients

Highlight box

Key findings

- One third of patients, 6–12 months following lung resection for non-small cell lung cancer (NSCLC), still reported increased dyspnoea.
- Female sex and extent of resection were associated with increase in dyspnoea 6–12 months after anatomic lung resection for NSCLC.

What is known and what is new?

- Dyspnoea is common after lung resection but literature does not characterise its incidence beyond the immediate postoperative period well, our study looks at its evolution in the late setting.
- Predicting the incidence of dyspnoea with objective respiratory measures can yield inaccurate results so we investigate factors associated with late postoperative dyspnoea.

What is the implication, and what should change now?

- Our results suggest that dyspnoea is common postoperatively even with minimally invasive approaches, but its evolution remains difficult to predict.
- Understanding peri-operative evolution of patient-reported dyspnoea is critical to foster shared decision making.
- We have demonstrated a place for standardised patient reported outcomes measuring dyspnoea within guidelines.

undergoing anatomic lung resection (lobectomies or segmentectomies) for NSCLC at the Department of Thoracic Surgery, St James's University Hospital, Leeds from September 2014 to December 2018 and with complete preoperative and postoperative (either 6 or 12 months) QOL assessment. All patient data was anonymised and linked to clinical records via encrypted identification.

Patient recruitment

Patients were selected for lung resection following a multi-disciplinary team (MDT) meeting that considered clinical variables, tumour status, and current clinical guidelines (7). Operability was assessed following current functional guidelines in relation to their pulmonary function test and exercise capacity (8). All patients undergoing lung resection with suspected histological malignancy were scheduled a preoperative consultation with a lung cancer specialist nurse. Patients were recruited during this consultation; after informed consent was taken, they were asked to complete and return the preoperative baseline Lung Cancer specific Quality of Life Questionnaire 13 (LC13) questionnaire at the appointment. Patients were non-consecutively selected as not every patient who attended preoperative consultations gave consent to be recruited. Patients undergoing neoadjuvant or adjuvant chemotherapy were not included in this study. Patients submitted to pneumonectomy were excluded at analysis as this extent of resection is associated with worse QOL following surgery (9).

Intervention details

All surgeries were led by a consultant thoracic surgeon and surgical access was either by video-assisted thoracoscopic surgery (VATS) approach or muscle-sparing thoracotomy. The types of anatomical lung resection performed were lobectomy and segmentectomy. A histological diagnosis of NSCLC was confirmed following resection. Factors taken into consideration in the type of resection were the size of tumour, the location of tumour and the performance status of the patient. Peri-operative factors were standardized according to standardised enhanced recovery care pathways (3). This included encouragement of early mobilization/oral food intake, intense chest physiotherapy, deep vein thrombosis (DVT) and antibiotic prophylaxis and pain management by patient-controlled analgesia (PCA).

Dyspnoea assessment

The European Organization for Research and Treatment (EORTC) published the LC13 in 1994 of which we utilised their Dyspnoea (LCDY) scale (10). The LC13 questionnaire was considered the gold standard instrument exploring QOL of patients with lung cancer at the time of study design, though it has now been updated (11). It assesses 13 core symptoms of lung cancer patients. We were interested in the LCDY scale of the module which assessed dyspnoea in three modalities: during rest, walking and climbing stairs in the preceding week. In each setting dyspnoea was quantified from 1 (not at all short of breath) to -4 (very much short of breath), therefore a higher score indicated a higher level of dyspnoea. The LCDY scale was used to quantify dyspnoea at the stages of interest, such as the preoperative and postoperative setting specifically at 1, 3, 6 and 12 months. A new variable called LCDY-late was generated, grouping measurements at 6 or 12 and imputing values from 6-month if the 12-month assessment included missing data. We decided to investigate the late effects of dyspnoea as demonstrated by other studies, patient-reported outcome measures (PROMs) after surgery tend to have a marked worsening immediately after surgery, to start recovering after 3–6 months afterwards (12).

Follow-up was conducted by clinic or by post and the questionnaire was completed on paper or online.

Statistical analysis

Our main objective was to test changes in dyspnoea perioperatively, so we looked at the clinically significant change (defined as a difference of >10 points) between LCDY score from the preoperative to late 6–12 months period (LCDY-late) (13,14). The dyspnoea score was linearly transformed to a 0 to 100 scale, where higher numbers indicated increased dyspnoea levels. Several baseline and operative variables were tested for a possible association with a clinically meaningful worsening in dyspnoea: age, gender (biological), body mass index (BMI), force expiratory volume in 1 second (FEV1), diffusing capacity of the lungs for carbon monoxide (DLCO), history of coronary artery disease, cerebrovascular disease (defined as history of stroke or transient ischaemic attack), diabetes, extent of resection (lobectomy *vs.* segmentectomy) and surgical access (minimally invasive *vs.* open).

The univariable association of each variable with

outcome was initially tested using a univariable logistic regression analysis for each covariate. Those variable with a P value of <0.1 at the univariable logistic regression analysis were used as predictors in a stepwise logistic regression analysis with backward elimination (P for retention in the final model <0.1). Baseline and surgical variables were entered in the regression model along with the preoperative LCDY value.

The analysis was performed using Stata 15.1 software (StataCorp; College Station, TX, USA).

Table 1 Baseline and surgical characteristics of the patients included in the study

Variables	Values
Age (years)	70.7 (9.1)
Gender (male)	55 [42]
BMI (kg/m ²)	27.2 (5.5)
FEV1 (%)	89.2 (21.6)
DLCO (%)	73.7 (17.7)
CAD	10 [7.6]
CVD	9 [6.9]
COPD	31 [24]
Diabetes	13 [10]
PS greater than 1	17 [13]

Results are expressed as mean (standard deviation) for numeric variables and count [percentages of total] for categorical ones. BMI, body mass index; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of the lungs for carbon monoxide; CAD, coronary artery disease; CVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; PS, performance status.

Table 2 Evolution of dyspnoea as measured by the LCDY scale over time

Timepoint	Number of patients	Mean LCDY score (SD)	Minimum LCDY	Maximum LCDY
Baseline	131	11.9 (16.9)	0	100.0
3 months postoperative	51	25.9 (17.3)	0	66.7
6 months postoperative	91	15.1 (19.1)	0	66.7
12 months postoperative	100	15.2 (18.8)	0	77.8
Combined 12 and 6 months (LCDY-late)	131	16.7 (19.5)	0	77.8

LCDY, Lung Cancer Dyspnoea Scale; SD, standard deviation.

Results

Our patient cohort consisted of 131 patients. Overall, 123 patients underwent VATS and 8 underwent muscle sparing thoracotomy. Of these, 109 underwent lobectomy and 22 underwent segmentectomy. In total, 131 patients completed LC13 questionnaire at a minimum of the preoperative and at least one postoperative stage (6 or 12 months). Ninety-one patients had complete measurements at 6 months and 100 patients at 12 months. None of the patients had early mortality.

The characteristics of the 131 patients included in the analysis are shown in *Table 1*.

More than half of patients were female (58%). Fifty-six percent of patients were older than 70 years and 13% younger than 60 years of age.

Table 2 and *Figure 1* reports the evolution of LCDY scale over time.

The mean preoperative LCDY score was 11.9 and the mean LCDY-late score was 16.7; equivalent to mild symptoms (patient self-report of ‘a little short of breath’ is equivalent to a score of 33.3 on a single item). Of all patients, 39 (30%) experienced a clinically meaningful deterioration (>10-point increase) in postoperative dyspnoea defined as an increase in LCDY score of greater than 10 from baseline to 6–12 months. Among the 29 patients with no dyspnoea (LCDY =0) at baseline, a clinically meaningful deterioration occurred in 21 patients (72%), with LCDY-late mean scores ranging from 11 to 66.7.

Fifty-two percent of patients younger than 60 experienced clinically significant dyspnoea, *vs.* 29% of those aged 60–74 years, and 22% of those aged 75 or older (P=0.060). Of all female patients 41% experienced a clinically significant change in dyspnoea compared to 15% of male patients (P=0.002). COPD was not associated with worse

postoperative changes in dyspnoea ($P>0.99$). Patients undergoing segmentectomies had better preservation of their preoperative breathing capacity hence only 9% experienced a clinically significant deterioration of dyspnoea *vs.* 34% after lobectomy ($P=0.021$). The surgical access (VATS *vs.*

muscle sparing thoracotomy) was not associated with a clinically significant reported late dyspnoea in our series ($P=0.700$) (*Table 3*).

Table 4 shows the results of the univariable logistic regression analysis for each covariate.

After adjusting for pre-operative LCDY score, female gender remained the only clinically significant factor associated with clinically meaningful increase in postoperative dyspnoea at 6–12 months following lung resection as reported by patients. A total of 34% of patients reported increased dyspnoea after lobectomy and 9% after segmentectomy ($P=0.014$). Therefore, lobectomy as opposed to segmentectomy showed a trend toward an increased risk of clinically meaningful deterioration in dyspnoea. Objective respiratory parameters such as FEV1 and DLCO were not associated with worsening perioperative changes in dyspnoea (*Table 5*).

There were no adverse events in our patient group.

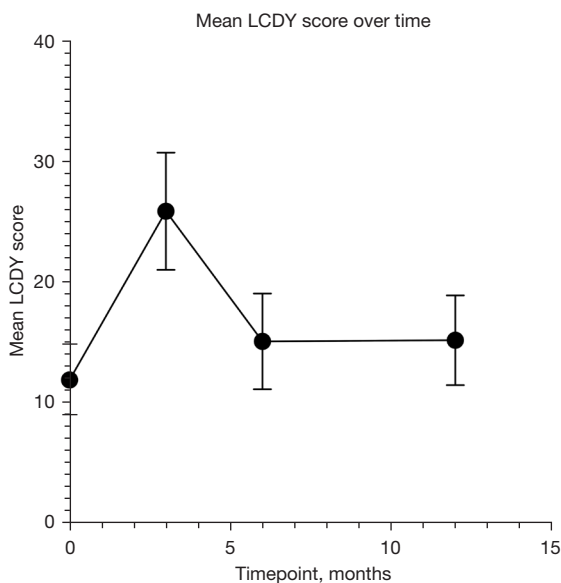


Figure 1 Evolution of self-reported dyspnoea following lung resection at different measurement times. LCDY, Lung Cancer Dyspnoea Scale.

Discussion

Key findings

In our cohort of patients undergoing anatomical lung resection for NSCLC, we found that dyspnoea was present in one third of patients, as they experienced a clinically meaningful increase in dyspnoea 6–12 months after surgery. However, the isolated postoperative dyspnoea score was

Table 3 Perioperative changes of patient reported dyspnoea by patients' category

Characteristics	Category	Number experiencing clinically significant increase in LCDY from baseline to 6–12 months [%]	P value
Age group (years)	≥75	10 [22]	0.060
	≥60, ≤74	20 [29]	
	<60	9 [52]	
Gender	Female	31 [41]	0.002
	Male	8 [15]	
COPD	No COPD	29 [29]	>0.99
	COPD	10 [32]	
Type of operation	Lobectomy	37 [34]	0.021
	Segmentectomy	2 [9]	
Surgical access (limited to segmentectomy and lobectomy)	Minimally invasive	36 [29]	0.700
	Open	3 [38]	

LCDY, Lung Cancer Dyspnoea Scale; COPD, chronic obstructive pulmonary disease.

Table 4 Results of the univariable logistic regression analysis (dependent variable: clinically meaningful changes of dyspnoea at 6–12 months after surgery)

Variables	Regression coefficient	SE	P value
Age (years)	−0.460	0.200	0.017
Gender (male)	−0.980	0.390	0.013
BMI (kg/m ²)	−0.120	0.030	0.720
FEV (%)	−0.001	0.008	0.900
DLCO (%)	−0.010	0.010	0.350
Baseline LCDY	−0.005	0.010	0.027
CAD	−0.710	0.810	0.390
CVD	−0.560	0.820	0.500
Diabetes	0.800	0.570	0.160
Open surgical access	0.550	0.570	0.340
Type of operation (segmentectomy as opposed to lobectomy)	−1.630	0.760	0.033

SE, standard error; BMI, body mass index; FEV, forced expiratory volume; DLCO, diffusing capacity of the lungs for carbon monoxide; LCDY, Lung Cancer Dyspnoea Scale; CAD, coronary artery disease; CVD, cerebrovascular disease.

Table 5 Results of the logistic regression analysis to identify factors associated with postoperative clinically meaningful changes in dyspnoea at 6–12 months after surgery

Variables	Regression coefficients	SE	P value	95% CI
Age (years)	−0.42	0.02	0.063	−0.090 to 0.002
Gender (male)	−1.17	0.46	0.011	−2.08 to −0.26
Baseline LCDY	−0.01	0.01	0.320	−0.04 to 0.01
Extent of operation (segmentectomy as opposed to lobectomy)	−1.45	0.79	0.067	−3.0 to 0.1

SE, standard error; CI, confidence interval; LCDY, Lung cancer Dyspnoea Scale.

equivalent to only mild symptoms, suggesting that lung resection is an effective treatment with regards to QOL. Future work could explore the threshold at which dyspnoea scores impact different elements of QOL such as social and role function. Furthermore, we were able to show that patients with no baseline dyspnoea reported worse symptoms as 71% of this group had a meaningful increase in dyspnoea following surgery. This may be because this group having never experienced dyspnoea report a more pronounced effect on their QOL. It would be interesting to study this patient group beyond 12 months to observe if they adapt to their dyspnoea. As well as absence of preoperative dyspnoea our results showed that female gender was associated with higher levels of postoperatively dyspnoea. In line with findings reported by other studies, decreased FEV1 and DLCO were not associated with

increased postoperative dyspnoea (15). We did not find an association between co-morbidities measured such as diabetes, COPD and dyspnoea within our patient cohort. However, we hope that our exploratory research raises interest of other factors which can affect dyspnoea in theory so we can start building an evidence base from investigation in larger cohort studies. Such factors should not be limited to co morbidities such as anaemia and may include anxiety, smoking status and pain.

Comparison with similar researches and explanations of findings

With growing populations of lung cancer survivors, it is important to extend the objective of treatment beyond survival to preservation of QOL. Rolke and colleagues

report that in patients receiving surgery as the first treatment modality for lung cancer, role function and dyspnoea worsened, but remained stable for patients treated with chemotherapy or radiotherapy (16). This highlights the importance of incorporating outcomes related to QOL into the field of thoracic surgery. This study investigated the evolution of dyspnoea following lung resection alongside associated factors. Living with dyspnoea can be debilitating, so patients request information about its incidence and severity following surgery. As we have entered an era of healthcare in which patients are empowered to take part in discussions regarding their care, the understanding of the evolution of dyspnoea must be consolidated. One method of doing this would be the incorporation of patient reported outcomes that are closely related to QOL into guidelines. This would standardise their collection while reducing the burden on clinicians of collecting supplementary information. In 2015 a survey conducted on members of the European Society of Thoracic Surgeons revealed that only 12% of members were incorporating patient reported outcomes into their clinical practice (17).

Dyspnoea is an important variable to measure following lung resection surgery. Gruenberg and colleagues report that severe self-reported dyspnoea was associated with significant impairment in health related QOL, work productivity and presentation to emergency services in COPD patients (18). This reflects the transformative impact that dyspnoea can have on lives of patients, reiterating the importance of understanding its evolution and associated factors. Postoperative impairment of pulmonary function is accepted due to removal of lung tissue, and some consider changes in chest wall mechanics due to surgical incision to be a contributory factor (19). Yet existing literature does not characterise dyspnoea after the immediate postoperative period well. In the present analysis we observed dyspnoea at the 6–12-month postoperative period. Future investigations should focus on longer follow-up assessment, although longer-term collection of data may be logistically challenging. Longer term follow-up data could support the integration of patient reported outcomes related to QOL into guidelines, which could lead to implementation by clinicians.

Our study identified increased clinically significant dyspnoea in patients who were female, of a younger age and who experienced no dyspnoea preoperatively. These associated factors should be investigated further to help clinicians define patient risk and better inform patients during discussions related to treatment decisions. We

observed that younger patients reported more dyspnoea, though this did not reach significance. We can hypothesise that younger patients may have higher psychological expectations of functional status, similar to those with no preoperative dyspnoea. Knowing this may enable clinicians to present the expectation of dyspnoea differently when consenting a younger or less frail patient, compared to an older and frailer person, for major lung surgery. Patients' personality traits or psychological state may also influence their subjective perception of dyspnoea such as those advanced lung cancer. It would be elucidating to perform analyses on such subgroups of patients to gain a deeper understanding of the factors that influence perception of dyspnoea. Objectively it remains unclear whether it is possible to predict the postoperative dyspnoea difference for lobectomy *vs* segmentectomy in terms of lung preservation as we found only marginal association in our study. Furthermore, further data should be collected to investigate dyspnoea levels between different segmentectomies and lobectomies types too which could inform discussions at MDTs.

Secondly, clinicians could offer intense pulmonary rehabilitation programmes to patients in high-risk groups who may benefit (20). Chest physiotherapy for COPD patients before lung resection has shown encouraging results (6). If dyspnoea can be feasibly reduced through prophylactic preoperative pulmonary rehabilitation, QOL and outcomes in response adjuvant therapies may improve. This is an area of research where we could see the fusion of thoracic surgery and oncological practice. This study did not measure patient activity levels or results from objective respiratory tests. Some pulmonary rehabilitation programmes use these measurements amongst others to select ideal candidates who may benefit most from intervention. Correlating LCDY score to objective respiratory scores may have highlighted their inaccuracy consolidating the rationale for our study and potential identification of ideal candidates for intervention. Currently, selection for pulmonary rehabilitation programmes uses a multifaceted approach considering many different factors from nutritional status to previous hospitalisations, which were beyond the remit of this study to measure (21). Nevertheless, perioperative dyspnoea assessment can be incorporated in future studies assessing possible effects of pre-rehabilitation programs, especially in the era of longer multimodality treatments plans.

Our study did not measure association between dyspnoea and outcomes to adjunctive therapies. Also,

increasing length of hospital stay may be associated with dyspnoeic patients which would present further risks such as healthcare associated infections (22). While this is not the objective of our study, it explains why patient reported dyspnoea is an important factor to be considered in NSCLC pathways. The analysis of such data would be an appropriate and interesting expansion to our study that should be encouraged.

Strengths and limitations

This study has potential limitations that may have impacted on the results.

All patients were recruited from a single centre however, this allowed care pathways to be standardised, so we did not observe the effect of confounders in our results. Non-consecutive recruitment may have increased sampling bias, making it more difficult to generalise from our findings as well as the relatively small sample size. However, this was unavoidable as gaining informed consent from patients gave them the right to decline participation. Ninety percent of our patient cohort were operated on using VATS methods. This preference is established in surgical practice, but we cannot rule out that the inclusion of more open procedures could have affected our results. However, our analysis did not find surgical access to be associated with changes in patient reported dyspnoea when pneumonectomy was excluded as a confounding factor. Similarly, we could explore LCDY scores following resection for benign pathology. Additionally, not all patients who filled in a baseline pre-operative assessment did so at every postoperative stage, but we found samples were a good representation of Leeds patients during comparison studies. Although, we had some missing data during the postoperative follow-up period these were in line with other published reports on the same patients whilst working with real world data as opposed to clinical trials (23). The study relied on voluntary help of medical staff, hence this translated to impossibility to calculate any consent rate and also in a lack of possible reminder system for the patients. This has been a possible explanation of the higher attrition rate especially at 3 months. While the LC13 questionnaire was developed years ago it was considered the gold standard for assessing patient reported outcomes for QOL during study design. We believe that we would have gained similar results from the novel LC29 questionnaire (24). Lastly, cardiopulmonary complications could impact the perception

of postoperative dyspnoea. Although we measured pre-operatively diagnosed co-morbidities, we did not collect any data on this aspect.

Conclusions

Our study showed that one third of our patients, 6–12 months following lung resection for NSCLC, still reported increased dyspnoea. Of the variables tested, only gender and marginally, age and extent of resection, were associated with increased risk of postoperative worsening of dyspnoea. In conclusion, our results suggest that dyspnoea is common postoperatively even with minimally invasive approaches, but its evolution remains difficult to predict. Through this study we hope we have demonstrated a place for standardised patient reported outcomes measuring dyspnoea within thoracic surgery guidelines. This would allow for more data collection as well as for subsequent results to be incorporated into clinical consultations so that we can partake in shared decision making with patients. Further investigation is warranted to investigate the relationship between postoperative dyspnoea and outcomes to adjunctive therapies.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Formal ethical approval was not required, and this study was classified as a service evaluation so did not require an NHS Research and Ethics Committee review. Informed consent was taken from all the patients.

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