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Title: Quality of life after VATS lung resection and SABR for early-stage non-small cell lung cancer: a Longitudinal Study

Authors & Affiliation:

Cecilia Pompili[1,2], Zoe Rogers[1], Kate Absolom[1,2], Patricia Holch[1,3], Beverly Clayton[1], Matthew Callister[4], Johnathan Robson[4], Alessandro Brunelli[4], Kevin Franks[4], Galina Velikova[1]

Institutions: 1. Section of Patient Centred Outcomes Research, Leeds Institute of Medical Research at St James's, Faculty of Medicine and Health, University of Leeds, Leeds/UK 2. Leeds Institute of Health Sciences, Faculty of Medicine and Health, University of Leeds, Leeds/UK 3. School of Social Sciences, Beckett University, Leeds/UK. 4. Leeds Teaching Hospital Trust, Leeds/UK

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Corresponding Author:

Cecilia Pompili

Section of Patient Centred Outcomes Research,

Leeds Institute of Medical Research at St James's

University of Leeds

c.pompili@leeds.ac.uk

St James' Institute of Oncology, Beckett Street, Leeds LS9 7TF. UK

Telephone: (+44) 0113 20 68939, Fax: (+44) 0113 2067438

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Abstract

Introduction: Video-assisted thoracoscopic (VATS) lung resection is the recommended curative treatment for early-stage non-small cell lung cancer (NSCLC). Patients considered at high surgical risk, are treated with stereotactic ablative body radiotherapy (SABR) as a lower morbidity alternative. This study aims to investigate the impact of SABR and VATS resection on patients' quality of life (QoL) over the first year after treatment.

Methods: A prospective longitudinal observational study recruiting early-stage NSCLC patients from a single UK centre. QoL was assessed with EORTC QLQ-C30 and Lung Cancer Module LC13 at baseline, 6 weeks and 3, 6 and 12 months post-treatment.

Results: From 01.03.2017 till 01.03.2018, 244/281 patients (87%) consented to participate**,** 225 (95 SABR and 130 VATS) were included in the analysis.

SABR patients had significantly worse baseline QoL scores than VATS patients, even after adjusting for preoperative clinical factors (C-30 Global Health mean: SABR=53.8, VATS=71.2; Physical Functioning mean: SABR=57, VATS=82.2; Fatigue mean: SABR=43.5, VATS=23.7; C30 Dyspnea mean: SABR=49.5, VATS=26.2). During the 12 months post SABR treatment patients' QoL scores remained stable. In the VATS group, there was a deterioration 6-weeks after treatment in Role, Physical, Social

Functions, Global Health, Fatigue, C30/LC13 Dyspnoea, Pain, Appetite loss, Constipation, LC13 Pain in Chest and Arms. The scores improved by 12 months without reaching the preoperative values.

Conclusions: Although QoL outcomes for SABR and VATS are not comparable due to different medical selection criteria, the QoL impact of the two treatments during the first year showed different trends which will inform patients and clinicians during decision-making discussions.

1 Introduction

Lung cancer is the third most common cancer in the UK, accounting for almost 13% of all new cancer cases (2017)(1). When Non-Small Cell Lung Cancer (NSCLC) is diagnosed at an early-stage (Stage I-II), surgical resection is the main guideline-recommended curative treatment, with five-year survival rates from 90% for Stage IA to 65% for Stage IIA(2). Open lung resection has been increasingly replaced by a minimal access video-assisted thoracoscopic surgery (VATS) resulting in reduced complications and faster recovery(3). However, some patients with Stage I-II cancers are not suitable for surgery due their age and/or poor fitness secondary to significant medical comorbidities. Indication for surgery have been defined by guidelines, including functional tests (cardio-vascular and respiratory function tests), performance status and patient's acceptance of perioperative risk (4). In 2017, the overall resection rates ranged from 13.0–30.4% between surgical trusts in England. Patients treated with surgery had good performance status of 0-1(5). Recently, patients with high surgical risk can be treated with stereotactic ablative body radiotherapy (SABR). SABR is an advanced technique where peripheral tumours are ablated using higher biologically equivalent doses than conventionally fractionated radiotherapy, providing improved overall survival with lower morbidity (6, 7). Patients undergoing SABR tend to be older, have more comorbidities and lower baseline health-related QoL than surgical patients(8).

Direct comparison of the clinical outcomes after VATS and SABR have been limited by the lack of high-quality randomised controlled trials (9). Such trials are inherently difficult to do in this patient population, due to significant co-morbidities and often poor performance status. However, robust information about the longitudinal QoL may

support patients during the preoperative decision-making, especially when the patient has borderline fitness and the patients has personal and social preferences.

Although guidelines recommend objective thresholds to estimate the surgical risk of lung resection(4) and thus counsel patients towards VATS or SABR, the main concern for patients is less the immediate risk of serious complications, but rather the permanent disability and loss of independence which impacts on patients' quality of life (QoL).

This study aimed to describe in detail the QoL of early-stage NSCLC patients before and during the first 12 months after VATS or SABR treatments, based on routine practice in one cancer centre, and using standard validated instruments. Specifically, we wanted to: 1) compare baseline QoL of patients treated with VATS versus SABR and 2) to describe the trajectories of QoL in the 12 months following each treatment. The hypothesis was that the two treatments would have different effects on patients' QoL over time. A secondary aim was to determine the feasibility and patient acceptability of collecting regular QoL and patient-reported outcomes data in clinical practice.

Material and Methods:

Study Design and participants

Life after Lung Cancer (Lilac), is a prospective observational longitudinal study utilising repeated QoL measures. Patients undergoing treatments for early-stage NSCLC, VATS or SABR, not involved in other QoL studies, were consecutively recruited from the Leeds Teaching Hospitals NHS Trust. The study received ethical approval from The National Research Ethics Service Yorkshire and the Humber-Leeds East

Committee (REC Ref: 16/YH/0407) and was registered in the Clinical Trial database (ClinicalTrials.gov Identifier: NCT02882750).

All participants provided written consent and were invited to self-report QoL measures using online secure access from home/clinic, or paper administration as an alternative. Full details of the study protocol and patient's perception of the QoL collection have been published (10, 11). Patients were identified by lung cancer teams through the multidisciplinary team meetings. Selection criteria were: diagnosis of NSCLC either from histology or tumour board agreement on >95% likelihood of diagnosis based on radiological evidence, decision for surgery or SABR and able to give informed consent. Exclusion criteria were: advanced stages, patient included in other QoL study (to avoid patient burden). The decisions to select early-stage NSCLC patients for surgical and SABR treatment were based on current lung cancer guidelines(12).

Quality of Life assessment

QoL data were collected with the European Organization for Research and Treatment (EORTC) Quality of Life Questionnaire (QLQ-C30) and its Lung Cancer specific Module (LC13) at baseline, post-treatment at 6 weeks, 3, 6 and 12 months (13, 14). The EORTC questionnaire responses were rated on a four-point Likert scale and transformed linearly to 0-100 scores. In function scales, higher scores indicate a higher level of functioning, while higher scores on symptom scales and single items indicate worse symptoms (13). Missing items were managed according to the EORTC guidelines(15). The summary score (0=worst to 100=best). was calculated according to Giesinger et al (16).

Statistical analysis

Baseline demographic and clinical characteristics

Descriptive statistics were used to present the baseline characteristics of the treatment groups. Between groups comparisons (VATS vs SABR) used independent t-test for numeric variables with normal distribution or Wilcoxon rank-sum test for those without normal distribution. Categorical variables were compared by using Chi-square or Fisher's exact test.

Questionnaire completion rates

At each time point we calculated proportions of completed questionnaires from those expected (excluding withdrawals or deaths). Potential reasons for missing data at baseline was explored descriptively by comparing the demographic and clinical characteristics of responders vs non-responders.

Baseline Quality of Life results and Quality of Life trajectory over time

Mean QoL scores and standard deviations were calculated for all QLQ-C30 and QLQ-LC13 scales and/or single items at all time points. To test if baseline QoL scores were associated with the treatment group we used initially univariate Generalised Linear Models (GLM), followed by multivariate models adjusting for age, gender, performance status and Forced Expiratory Volume in one second (FEV1%).

The trajectory of QoL scores are presented graphically for all functional and symptom scales of EORTC QLQ-C30, and LC13 symptoms. Clinically meaningful differences over time on a group level were considered to be ≥10 points for EORTC QLQ-C30 scales(17). For the Summary score and LC13 scales, where no recommendations exist, a change of ≥ ½ SD (calculated for each individual measure at baseline across both VATS and SABR groups) was considered as clinically meaningful(18).

All analyses were exploratory in nature, thus significant p-values ($p < 0.05$) should not be interpreted as confirming a priori hypothesis. The analysis was performed on Stata 15.0 statistical software (Stata Co., College Station, TX).

This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines(19). We have also followed the Consolidated Standards of Reporting Trials (CONSORT) Patient Reported Outcome (PRO) guidance for the reporting the QoL results(20).

Results

From 01.03.2017 till 01.03.2018, 403 patients were screened, 47 were not eligible, of the remaining 356, 75 were not approached due to staff shortage; 244/281 approached patients (87%) consented to participate to the study (Figure 1).

A further 19 in the surgical group were excluded (did not receive any treatment after consenting or had open procedures). Therefore, 225 patients were included in the final analysis (95 SABR; 130 VATS). 44 patients left the trial over the course of the follow up period: 23 patients died (13 in the SABR group; 10 in Surgery); nine patients became ineligible during the course of the follow up (had standard radiotherapy) and 12 patients (8 SABR patients and 4 VATS) actively withdrew (too much going on n=5, n=7 did not provide a reason).

Patient Baseline Demographic and Clinical Characteristics (pre-and post-treatment)

As expected, the two groups differed considerably in their clinical pre-treatment features (Table 1). SABR patients were older than the surgical group [mean age (SD) 74.3 (9.20) and 70.0 (8.84) respectively]; had significantly worse respiratory parameters; worse performance status (57% had Eastern Cooperative Oncology

Group (ECOG) Performance Score >1 vs 16% of VATS patients) and more co-morbidities.

Analysis of post-treatment complications demonstrated that patients treated with SABR experienced more Grade 1-2 complications, as defined by the Common Terminology Criteria for Adverse Events-CTCAE (21), but there was no difference in the rate of major complications (grade 3-5). No statistical difference has been found in 90 days and 1-year mortality rates.

Table 1: Baseline demographic and clinical characteristics and rates of post-treatment complications.

Clinical variable	SABR (N=95) Mean (SD) or Count (%)[e]	VATS (N=130) Mean (SD) or Count (%)	p value[f]
Age	74.3 (9.20)	70 (8.84)	0.0001
Sex male (n,%)	37 (39%)	62 (48%)	0.21
FEV1 %[a]	76.6 (26.34)	88.0 (22.35)	0.0001
DLCO %[b]	71.0 (22.13)	83.4 (21.09)	< 0.0001
Charlson Comorbidity Index[c]	2.1 (1.31)	1.2 (1.00)	< 0.0001
ECOG Performance Score >1 (n,%)	54 (57%)	21 (16%)	< 0.0001
Coronary Artery Disease (n,%)	32 (34%)	9 (6.9%)	< 0.0001
Cerebrovascular Disease (n,%)	12 (13%)	4 (3.1%)	0.008
Chronic Kidney Disease (n,%)	7 (7.4%)	1 (0.8%)	0.011
Diabetes (n,%)	22 (23%)	10 (7.7%)	0.001
Chronic Obstructive Pulmonary Disease (n,%)	44 (46%)	38 (29%)	0.009
Tumour size (cm)	2.1 (0.99)	2.5 (1.41)	0.097
Pre-treatment path diagnosis (n,%)	38 (40%)	74 (57%)	0.1
All Complications (n,%)	85 (89%)	95 (73%)	0.002
Minor Complications (Grades 1-2)[d]	64 (67%)	68 (52%)	0.028
Major Complications (Grades 3-5)[d]	21 (22%)	27 (21%)	0.809
Treatment related deaths within 90 days (n,%)	3 (3.2%)	7 (5.4%)	0.52
Deaths at 1 year (n,%)	14 (15%)	11 (8.5%)	0.14

a. Forced expiratory volume in 1 second (FEV1)

b. Carbon monoxide lung diffusion capacity (DLCO)
c. Charlson Comorbidity Index (CCI) ranged from 0 (low risk) to 7 (higher risk) of death in 1 year from comorbidities; derived from electronic patient records
d. Complications defined by the Common Terminology Criteria for Adverse Events (CTCAE); derived from electronic patient records
e. Results expressed as mean and standard deviation for numerical variables or count and percentages for categorical variables.
f. p-value from independent t-test for numerical variables with normal distribution or Wilcoxon rank-sum test for those without normal distribution. Categorical variables were compared using the Chi-squared test or the Fisher's exact test.

192

193 *Questionnaire completion rates*

194

195 SABR patients were more compliant with baseline completion of QoL questionnaires
196 (78%) versus only 54% compliance by VATS patients (Fig 2). The low completion by
197 patients planned for VATS was likely due to the short time patients had between the
198 decision for surgery (at one-stop clinic) and the surgical procedure. In order to examine
199 any patterns of missing baseline data, we compared QoL responders vs non-
200 responders both in VATS and SABR groups (Suppl 2). No differences were seen in
201 terms of age (VATS p=0.16; SABR p=0.85), gender (VATS p=0.36; SABR p=0.075),
202 FEV1% (VATS p=0.48; SABR p=0.09), DLCO (VATS p=0.35; SABR p=0.66), or
203 ECOG PS (VATS p=0.77; SABR p=0.79). Therefore, we assume the data is missing
204 at random rather than any group characteristics, but this high rate of missing baseline
205 data reduces the power of the subsequent analysis during follow-up. Completion rates
206 at 6 weeks, 3,6 and 12 months are similar for SABR and VATS, mid-60% to low 70%
207 of expected. Only 12% of patients (27/225) opted for the online completion of the QoL
208 questionnaires (VATS 20/130,15.4%; SABR 7/95, 7.4%, p=0.095).

209

210 *Baseline Quality of Life results*

211 SABR patients had worse baseline scores than VATS patients on most of the
212 functional and symptom scales, except Emotional Functioning, Insomnia, Diarrhoea,
213 Financial difficulties, Haemoptysis, Alopecia, Dysphagia, Sore Mouth and Pain (LC13)
214 (Table 2). The size of the differences in means was between 10 and 20 points,

indicating they are clinically meaningful. These differences were expected due to the guidelines-based selection of patients with poor clinical characteristics to be offered SABR. Indeed, when adjusted for the known clinical factors (age, gender, performance status and FEV1), only Global Health, Physical Functioning, Fatigue, and Dyspnoea (QLQ-C30) remained significantly associated with treatment group (SABR group having worse scores).

Table 2. Comparison of baseline QoL scores.

Variable	SABR Mean (SD)[a]	VATS Mean (SD)	GLM N[b]	Unadjusted standardised coefficient of association with treatment type[e] β (95% CI)	p-value	GLM N	Adjusted standardised coefficient of association with treatment type[e] β (95% CI)	p-value	Adjusted for[f]
Baseline QLQ-C30 Global health and functional scales[c]									
Global Health	53.8 (23.58)	71.2 (16.65)	144	0.39 (0.24 – 0.54)	< 0.001	127	0.20 (0.02 – 0.37)	0.03	FEV1 p=0.07 PS p<0.02
Physical Function	57.0 (23.34)	82.2 (17.88)	144	0.52 (0.38 – 0.66)	< 0.001	127	0.28 (0.11 – 0.44)	0.001	FEV1 p=0.006 PS p=0.002
Role Function	63.1 (31.61)	83.6 (23.48)	144	0.35 (0.19 – 0.50)	< 0.001	127	0.13 (-0.05 – 0.32)	0.15	FEV1 p=0.03 PS p<0.03
Emotional Function	66.4 (29.78)	73.6 (25.46)	144	0.13 (-0.03 – 0.29)	0.12	136	-0.02 (-0.20 – 0.17)	0.87	PS p=0.02
Cognitive Function	73.0 (26.70)	83.1 (18.50)	144	0.21 (0.05 – 0.38)	0.009	127	0.09 (-0.10 – 0.29)	0.36	FEV1 p=0.39 PS p=0.28
Social Function	63.5 (35.72)	82.9 (21.42)	144	0.31 (0.16 – 0.47)	< 0.001	127	0.12 (-0.06 – 0.31)	0.20	FEV1 p<0.09 PS p=0.07
Summary Score	70.3 (18.80)	83.1 (13.87)	142	0.36 (0.21 – 0.51)	< 0.001	126	0.15 (-0.03 – 0.33)	0.11	FEV1 p=0.10 PS p=0.02
Symptom scales/items[d]									
Fatigue	43.5 (26.04)	23.7 (19.47)	143	-0.40 (-0.55 – -0.25)	< 0.001	126	-0.20 (-0.38 – -0.02)	0.03	FEV1 p=0.14 PS p=0.07
Nausea/Vomiting	8.8 (15.90)	3.8 (10.68)	144	-0.18 (- 0.34 – -0.02)	0.03	127	-0.07 (-0.27 – 0.13)	0.47	FEV1 p=0.31 PS p=0.37
Pain	25.5 (29.22)	11.4 (19.97)	144	-0.27 (- 0.43 – -0.11)	0.001	127	-0.01 (-0.19 – 0.18)	0.92	FEV1 p<0.03 PS p=0.008
Dyspnoea	49.5 (31.33)	26.2 (25.94)	144	-0.38 (- 0.53 – -0.22)	< 0.001	127	-0.20 (-0.39 – -0.01)	0.04	FEV1 p=0.31 PS p=0.005
Insomnia	33.8 (34.47)	32.9 (33.81)	143	-0.01 (- 0.18 – 0.15)	0.87	-	-	-	-
Appetite loss	23.4 (31.08)	11.9 (24.76)	144	-0.20 (- 0.36 – -0.04)	0.01	136	-0.13 (-0.31 – 0.05)	0.17	PS p=0.16
Constipation	20.3 (29.10)	11.0 (23.89)	144	-0.17 (-0.33 – -0.01)	0.04	135	-0.11 (-0.30 – 0.08)	0.26	Age p=0.16 FEV1 p=0.37
Diarrhoea	8.6 (19.94)	4.8 (14.23)	144	-0.11 (-0.27 – 0.05)	0.19	-	-	-	-
Financial problems	13.2 (24.05)	8.6 (21.75)	143	-0.10 (-0.27 – 0.06)	0.22	-	-	-	-
QLQ-LC13 Symptom scales/items[d]									
Dyspnoea	36.9 (26.91)	20.8 (22.09)	132	-0.31 (-0.47 – -0.15)	< 0.001	115	-0.01 (-0.21 – 0.19)	0.92	FEV1 p<0.02 PS p=0.001
Coughing	43.7 (30.65)	28.3 (26.95)	137	-0.26 (-0.42 – -0.10)	0.002	120	-0.11 (-0.33 – 0.10)	0.31	FEV1 p=0.24 PS p=0.26
Haemoptysis	2.3 (13.00)	2.0 (9.92)	137	-0.01 (-0.18 – 0.15)	0.87	-	-	-	-
Sore mouth	13.6 (28.50)	6.7 (18.82)	136	-0.14 (-0.31 – 0.03)	0.1	119	-0.03 (-0.25 – 0.19)	0.79	FEV1 p=0.28 PS p=0.18
Dysphagia	10.0 (22.95)	4.0 (14.92)	136	-0.15 (-0.32 – 0.02)	0.07	-	-	-	none significant in univariate
Peripheral neuropathy	16.2 (27.31)	7.1 (18.04)	134	-0.19 (-0.36 – -0.03)	0.02	117	-0.05 (-0.24 – 0.15)	0.64	FEV1 p=0.65 PS p=0.26
Alopecia	3.8 (12.10)	1.0 (5.80)	135	-0.14 (-0.31 – 0.02)	0.09	126	-0.06 (-0.25 – 0.13)	0.54	Gender p=0.33 FEV1 p=0.47
Pain in chest	16.7 (23.23)	8.2 (17.71)	135	-0.20 (-0.37 – -0.03)	0.02	119	-0.01 (-0.21 – 0.19)	0.91	FEV1 p=0.78 PS p<0.001
Pain in arm	20.4 (29.79)	10.9 (23.35)	123	-0.18 (-0.35 – -0.00)	0.05	115	-0.12 (-0.33 – 0.09)	0.25	FEV1 p=0.34
Pain other	30.6 (36.97)	21.7 (28.67)	120	-0.13 (-0.31 – 0.04)	0.14	-	-	-	-

a Standard deviation for mean scores.
b Some data missing due to patients not completing all questionnaire items.
c Higher scores for measures of global health, summary score and functional scales indicate better health.
d Higher scores for symptom scales/items indicate worse symptom effect on patients.
e Univariate and multivariate analyses carried out using generalised linear model (GLM) due to non-parametric dependent variables
f Non significant variables (from gender, age, FEV1 and performance score) in univariate analyses not adjusted for in multivariable analysis

Quality of Life trajectory 12-months after treatment

Figure 3 shows the changes in functional and symptom scales (EORTC QLQ-C30 and LC13) over 12 months from baseline. Supplementary Table 3 presents details on mean scores, SD and patient numbers. SABR patients, who have started with worse baseline scores, maintained overall stability over 12 months across all functions and symptoms. It should be noted that patients reported the most impairment in Global Health, Physical and Role function (Figure 3a, low scores), and most severe symptoms (high scores) on Cough (3c), Dyspnoea (3b and 3c) and Fatigue (3b). At the post-treatment timepoint of 6 weeks, used to examine potential toxicity from SABR, a slight deterioration was seen in Role function, Dyspnoea and Cough. Those parameters returned to pre-treatment values by 3 months. General Pain (QLQ-C30) showed a trend for late worsening between 3 and 12 months, only Emotional Function improved from baseline to 3 months by a clinically meaningful amount (>10 points, Suppl 3). QLQ-C30 Summary score, being a composite measure of functioning and symptomatology, remained stable during all time points.

VATS patients, who had relatively good functioning and less symptoms at baseline, reported clinically significant deterioration at 6 weeks, the first timepoint after the surgery. Most deterioration was seen in Role, Physical, Social Functions, Global Health (3d), as well as Fatigue, Dyspnoea, Pain, Appetite loss, Constipation (3e), Dyspnoea and Pain in Chest and Arms (3f). In the subsequent reports at 3, 6 and 12 months the scores improved (suggesting a recovery of post-operative problems), but without regaining baseline levels. Role Function, Pain, C30 Dyspnoea, and LC13 Alopecia remained lower than baseline by a clinically meaningful amount. The

composite measure of QLQ-C30 Summary score, showed clinically meaningful deterioration at 6 weeks, with recovery afterwards, without reaching baseline scores. Although SABR patients functioning, lung symptoms (dyspnoea, cough, chest pain) and fatigue were stable over time, their severity levels remained worse than those of VATS patients over the 12 months period.

To aid the clinical interpretation of the results, a post-hoc descriptive responder analysis of change scores on individual level was performed for QLQ-C30 Global Health, LC13 Chest Pain and LC13 Dyspnoea (Suppl 4).

Discussion

In this prospective longitudinal cohort study, conducted in a real-world setting, we successfully recruited >60% of patients diagnosed over 12 months in a single cancer centre in UK with early stage NSCLC and treated with VATS resection or SABR. Consent rate for the study was over 80%, confirming its acceptability from patient perspective. There were challenges with completion of baseline questionnaires prior to surgery (response rate just over 50%) but overall compliance in the SABR group and post-baseline in the VATS group were in the mid-60% to low-70 percent. Online completion was not acceptable in this setting. Patients who were selected for SABR had, as part of their treatment selection criteria, more functional impairment and more symptoms at baseline. There was little impact of radiotherapy-related toxicity at 6 weeks, and all QoL scores showed little change in the first year after treatment. Our results can inform future patients that the majority of patients have stable functioning, symptoms and quality of life after radiotherapy (Suppl 4). The trajectory of functioning and symptoms was different in the VATS group, with deterioration in global health, functioning and symptoms immediately after surgery (6 weeks) with steady

improvement up to 12 months that did not reach pre-treatment levels. Our study will ultimately support the preoperative decision-making process, enabling clinicians to inform patients about the evolution of their quality of life after these treatments.

To the best of our knowledge, our study is one of the first to capture QoL trajectories in early-stage NSCLC patients in a real-world setting, following both VATS and SABR. As the baseline characteristics of the patients differ by definition, the purpose of analysis was primarily to provide information about the trajectory of quality of life in these two populations rather than draw direct comparisons between them.

Recent literature focuses on the clinical comparative effectiveness of surgical resection versus SABR and the impacts of each on QoL(8). Supporting our results, a study assessing 184 SABR and surgical patients using the Surveillance, Epidemiology, and End Results Medicare Health Outcomes Survey (SEER-MHOS) data set (22), showed that the only significant differences between the two groups were baseline physical and mental QoL, with SABR patients having worse QoL in both areas. There was no QoL differences between groups one year after treatment, but QoL was assessed with a generic health instrument SF-36 one year before diagnosis and one year after. Previous studies (23) reported that in general the physical components of QoL worsen immediately after surgery for up to 3-months, returning to baseline after 1 year. Avery and colleagues(24) in a recent QoL study of 92 VATS lobectomy patients over the first year, found a similar trend in patient-reported symptoms: patients experienced higher degrees of symptoms immediately after surgery without full recovery 12 months post-surgery. Similarly to them, we have confirmed in our VATS cohort findings a considerable impact of surgery on patients' QoL which is not fully recovered 12 months post-surgery, despite a minimally-invasive approach.

The baseline scores of the Global Health QoL in the two groups were, as expected very different. This reflects the observational, real-world approach adopted here as opposed to a formal RCT comparing the two treatments within a similar clinical group. Having the most compromised cardio-respiratory values, the lower baseline QoL scores of the SABR patients reflect this difference. Consistent with other studies (8), the baseline Global Health scores of SABR patient were lower (mean of 53.8, SD 23.58) than the recently published UK population normative data (mean of 62.3, SD 23.7), whereas the patients selected for VATS had higher scores (71.2, SD 16.65) (25). When we adjusted for the clinical variables, included the fitness selection (such as FEV1 and ECOG performance status), the difference in some scales persisted, indicating that the self-reported quality of life brings extra information. Future research should explore this issue to consider the addition of QoL domains to the clinical guidelines for patient selection.

Limitations

This real-world study has limitations to be considered when interpreting the results. Conducting a prospective observational study in a functionally impaired population and at the time of receiving a stressful, potentially life-threatening diagnosis is challenging. A major limitation is the different completion rates of the baseline questionnaires across the two treatment groups, with almost 50% missing data form VATS patients. The data appeared to be missing at random, but still this limits the number of patients for whom a meaningful longitudinal analysis can be performed. This is further impacted by the attrition over time for clinical reasons or non-return of QOL questionnaires. In our study, with the exception of the VATS patients at baseline, the questionnaire completion rates were comparable to other studies (26, 27). A recent

review on QoL assessment in early stage NSCLC patients revealed particular difficulties with the pre-treatment assessment, hampering effectiveness analysis (23).

With new UK lung cancer screening studies (Yorkshire Lung Screening Trial and Manchester Early Detection of Lung Disease) more early stage NSCLC may be diagnosed, with an increased incidence of early-stages NSCLC in an ageing population with comorbidities. For these higher risk patients, it is not known whether VATS or SABR are the best approach for an individual patient. The failure of previous feasibility trials in this setting has limited the evidence available(28) so our results will complement the available clinical findings.

Conclusions

The Lilac study successfully recruited 244 patients in a prospective longitudinal study with repeated QoL assessments. Although starting from a lower QoL, majority of patients have stable functioning, symptoms and quality of life after SABR. Patients undergoing VATS lung resection experienced a deterioration in global health, functioning and symptoms immediately after surgery (6 weeks) with steady improvement up to 12 months but not reaching pre-treatment levels. These data will further inform patients during the preoperative decision-making process of early-stage NSCLC.

Figure Legends:

Figure 1. Lilac study CONSORT diagram

Figure 2: Completion rates of QoL questionnaires

Figure 3: Trajectory of QoL scales over time.

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Supplementary files

S1: STROBE Checklist

S2: Responder to baseline questionnaire completion Analysis

S3: Means and SD confidence intervals for EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaire scores at each assessment time point for patients undergoing VATS and SABR. Higher scores for measures of global health and functional scales indicate better health/function. Bold numbers indicate a change in score from baseline of >10 points for C30 health/functions or >½ SD points for C30 Summary Score and are considered clinically relevant. Higher scores for symptom scales/items indicate an increased effect of these symptoms on patients. Bold numbers indicate a change in score from baseline of >10 points for C30 symptoms or >½ SD points for LC13 symptoms and are considered clinically relevant.

S4: Responder Analysis of QoL scores

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