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Patient-reported EORTC QLQ C-30 Global Health Status decline predicts survival after Video-assisted Thoracoscopic (VATS) lung resection and Stereotactic Ablative Radiotherapy (SABR): a 5 year follow-up from the Lilac study

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Abstract

Background: Early-stage non-small cell lung cancer (NSCLC) is increasingly treated with either video-assisted thoracoscopic surgery (VATS) or stereotactic ablative radiotherapy (SABR). While survival outcomes of these modalities have been widely studied, the prognostic significance of patient-reported outcomes (PROs), particularly short-term changes in global health status, remains underexplored in radically treated early-stage disease.

Methods: The Life after Lung Cancer (LiLac) study is a prospective observational cohort evaluating quality of life (QoL) trajectories in patients with clinical stage I-II NSCLC treated with VATS or SABR. QoL was assessed using the EORTC QLQ-C30 and LC13 at baseline and at 6 weeks, 3, 6, and 12 months. This analysis includes a 5-year survival follow-up of stage IA patients with available baseline and 6-week global health (GH) scores. Overall survival (OS), event-free survival (EFS), and lung cancer–specific survival (LCSS) were examined. A Fine–Gray competing risks model was used to identify predictors of lung cancer–specific mortality.

Results: A total of 142 patients were included (80 VATS; 62 SABR), with a median follow-up of 59 months. OS and EFS at 5 years were higher in surgical patients, while LCSS showed a favourable trend for VATS. A GH score decline >10 points at 6 weeks were the only factor independently associated with lung cancer–specific death (SHR

5.77, p=0.019), irrespective of treatment modality. No other QoL scales showed prognostic significance.

Conclusions: Early decline in patient-reported global health status after curative treatment for stage I NSCLC is a strong independent predictor of lung cancer–specific mortality. These findings support the integration of routine PRO assessment to inform risk stratification, recovery monitoring, and shared decision-making. Multicentre validation is warranted.

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 2023 in England, 37% of people diagnosed with lung cancer were diagnosed with stage I-II, with an overall resection rates increase up to 20%(5).

Patients with higher surgical risk can be treated with stereotactic ablative body radiotherapy (SABR). SABR is an advanced technique where 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 and as demonstrated in the SABRTOOTH trial(10), patients have a pre- pre-existing treatment preference that makes randomisation difficult(11).

Although guidelines recommend objective thresholds to estimate the surgical risk of lung resection(12) 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)(13).

The Lilac study describe in detail the QoL of early-stage NSCLC patients before and during the first 12 months after VATS resections or SABR treatments, based on routine practice in one cancer centre, and using standard validated instruments. 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. Previously published results suggested that collecting QoL data in this setting is feasible, and that surgery leads to greater short-term declines in quality of life, whereas SABR is associated with less acute deterioration, indicating better short-term tolerability(14).

However, given the well-recognised challenges in recruiting patients to randomised controlled trials in this setting, the prospectively collected data from this cohort therefore provided a valuable opportunity to explore survival outcomes and compare prognostic factors between treatment groups.

The objective of this analysis was to assess the 5-years survival limited to patient with clinical stage IA NSCLC and its relationship with peri-treatment changes in QoL.

2. Material and Methods:

2.1 Study Design and participants

Life after Lung Cancer (Lilac), is a prospective observational longitudinal study utilising repeated QoL measures. Patients undergoing treatments for stage I-II 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 main results have been previously published (14-16). 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: stages III-IV, 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(17).

2.2 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) pre-treatment, post-treatment at 6 weeks, 3, 6 and 12 months (18, 19).

EORTC QLQ-C30 includes 9 multi-item scales; five functional scales: physical, role, emotional, cognitive, and social functioning, three symptom scales: fatigue, pain, and nausea and vomiting, and a global health status/QoL scale. Six single-item scales assess symptoms: dyspnoea, appetite loss, sleep disturbance, diarrhoea, and financial impact. Scale scores are transformed to a 0–100 range, with higher scores indicating better functioning for functional scales, and greater symptom burden for symptom scales.

2.3 Statistical analysis

2.3.1 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.

2.3.2 Survival Analysis

The survival analysis was restricted to patients with clinical stage IA NSCLC only according to the eight edition of the TNM stage classification for lung cancer(20).

Overall survival (OS), Event-free survival (EFS) and Lung Cancer Specific Survival (LCSS) were assessed. Overall Survival (OS) was measured from the date of treatment completion to the date of death from any cause and censored at the date of last follow-up for survivors. Event-free survival (EFS) was measured from the date of treatment completion to the date of death from any cause or lung cancer recurrence, whichever occurred first, and censored at the date of last follow-up for survivors

without recurrence. LCSS was measured from the date of treatment completion to the date of death from lung cancer, and censored at the date of last follow up for survivors or deaths due to causes other than lung cancer

A Fine–Gray competing risks model was performed to identify factors associated with lung cancer specific death where the competing risk factors were deaths due to causes other than lung cancer such as non-cancer related deaths or cancer other than lung cancer related deaths). Stepwise regression model with backward elimination was used using a p value<0.1 for retention in the model. The following factors were initially entered in the competing regression model: age, sex, FEV1, DLCO, type of treatment (surgery vs. radiotherapy), history of coronary artery disease (CAD) or cerebrovascular disease (CVD), Performance Status (PS), Charlson's Comorbidity Index (CCI), General Health from the QLQ-C30 (GH) at baseline and at 6 weeks.

Statistical analyses were performed using the Sta 15.1 statistical software (Stata Corp, College Station, TX).

This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines(21). We have also followed the Consolidated Standards of Reporting Trials (CONSORT) Patient Reported Outcome (PRO) guidance for the reporting the QoL results(22).

3. Results

Of 403 patients screened from 01/03/2017 until 01/03/2018, 47 were not eligible and 75 were not approached due to staff shortages. Of the remaining 281 patients approached, 244 (87%) consented to participate in the study (Supplementary Figure 1).

Of the 244 patients consenting to LiLAC, 142 underwent treatment for clinically diagnosed stage IA NSCLC and are included in this survival analysis. 80 underwent Surgery and 62 SABR. Median follow up is 59 months (IQR 30-85).

The characteristics of the patients included in this analysis are presented in Table 1. As expected, patients treated with SABR were older, with more compromised pulmonary function and co-morbidities.

Median follow up in this series was 59 months (IQR 30-85). Overall survival (OS) at 5 years was 55% (95% CI, 43–65) for surgery and 37% (95% CI, 25–49) for SABR (log-rank p<0.001) (Fig 1). Surgery was associated with improved OS compared with SABR (HR 0.57, 95% CI 0.33–0.79; p = 0.003).

Event-free survival (EFS) at 5 years was 52% (95% CI, 41–63) for surgery versus 35% (95% CI, 24–47) for SABR (log-rank p < 0.001)(Fig 2), with a hazard ratio for surgery of 0.57 (95% CI, 0.37–0.87; p = 0.009).

Lung cancer–specific survival (LCSS) at 5 years was 82% (95% CI, 70–89) for surgery and 69% (95% CI, 53–80) for SABR (log-rank p = 0.0086). Surgery was associated with a trend toward improved LCSS compared with SABR (HR 0.51, 95% CI 0.24–1.10; p = 0.069) (Fig.3)

69 patients included in this analysis had both the baseline and six weeks EORTC QLQ-C-30 Global Health Status/QoL (GH) score measured.

The baseline GH status was higher in the surgical patients compared to those treated with SABR (72.2, SD 18.0, vs. 56.7, SD 25.2, p=0.0064). However, the average decline at 6 weeks was similar in the two groups (5.7, SD 16.0, and 4.6, SD 24.1, in the surgical and SABR groups respectively, p=0.88). The overall average peri-treatment difference in GH status at 6 weeks was 5.0 (SD 20). 23 patients had a decline in GH status greater than 10 (11 had surgery and 12 had SABR, p=1).

Competing regression analysis (where the competing risk was death for causes other than lung cancer) showed that the only factor associated with lung cancer specific death was 6 week decline in GH status greater than 10 (table 2) (SHR 5.8, p=0.019). Patients with a GH decline greater than 10 at 6 weeks have a 5.8 risk of dying of lung cancer compared to those without this decline independent of the treatment received. Figure 4 shows the cumulative incidence of lung cancer deaths ~~i~~n patients with and without a decline in GH greater than 10 in the two treatment groups. The presence of a large decline in GH was associated with higher incidence of lung cancer deaths in both treatment groups.

Peri-treatment changes in all other EORTC C-30 scales and Summary Score were independently tested and none of them was found associated with lung cancer specific survival (data not shown).

When baseline scales were individually tested in a competing regression analysis together with other patient related factors, only a lower summary score (SHR 0.97, p=0.016), emotional functioning score (SHR 0.98, p=0.008), and cognitive functioning score (SHR 0.98, p=0.001) were associated with higher risk of lung cancer specific death. No other baseline scale was associated with lung cancer specific death.

4. Discussion

In this long term follow-up analysis, conducted in a real-world setting, we demonstrated that in patients with stage IA NSCLC, 6 weeks decline in patient-reported EORTC QLQ-C-30 Global-Health Status/QoL score greater than 10 was associated with a 5.8 fold higher risk of dying of lung cancer irrespective of the curative treatment (VATS resection or SABR).

In this cohort of patients with stage IA NSCLC, surgical resection was associated with improved overall and event-free survival compared with SABR at 5 years. However, Lung Cancer Specific-survival was similar between the two groups, with more than 70% of patients remaining alive being recurrence-free at 5 years irrespective of treatment modality. From a quality-of-life perspective, we have previously reported that surgery has a more pronounced early impact, with significant short-term decline in global health and functioning, although most patients gradually returned to baseline levels over time. By contrast, SABR was associated with less acute deterioration, reflecting a more favourable short-term tolerability profile(15). Although this is not a randomized trial and several preoperative variables could not be assessed, our results are in line with the recently published data from the Revised-STAR trial showing progression-free survival between groups was also similar in the SABR and VATS Lobectomy and Mediastinal Lymph Node Dissection (VATS-L-MLND) groups at 5 years (77%, 68–87 vs 80%, 71–90; log-rank p=0·57)(23) and more comprehensive meta-analysis (24).

Increasing number of studies have been published underscoring the prognostic value of patient-reported outcomes in cancer care, incentivising an increased focus and more accurate information on issues that matter to patients(25).

At the same time, more methodological rigour has been advocated with recommendations aimed at improving the quality of future prognostic factor research, taking into consideration the unique challenges in QoL setting(26).

Few studies have investigated the added value of baselines and changes in QoL over time in advanced NSCLC setting, confirming the role of EORTC QLQ-C30 scores in predicting cancer-specific survival(27-30).

Nevertheless, the conclusions on the generalizability of QoL as prognostic of overall survival remain limited since these analyses were often exploratory and focused on advanced setting. Furthermore, in radically treated patients, the short-term evolution of QoL could improve the predictive accuracy, capturing potential treatment acute side-effects that are not easily and accurately assessed by the toxicity grading, especially in surgically treated patients. The current study investigated whether short-term changes in QoL scores from baseline over time were associated with survival independently from treatment in a cohort of early-stage NSCLC. Initial reports by Farrugia et Al. in patients treated with SABR at 3 months after SABR found that changes in global health status, functional QoL performance, and symptom burden, were associated with progression-free survival and overall survival outcomes(31). In the thoracic surgical setting, higher patient-reported physical function score has been demonstrated to be associated with longer overall survival after resection(32).

We selected a 10 points as minimally important difference (MID) to categorize the change in HRQOL score to include in the regression as being commonly recommended, including recently updated guidelines (33, 34).

Furthermore, a recently published meta-analysis in lung cancer patients reported for every 10-point increase in scores on the global quality of life, physical functioning, and

role functioning, there was a 13%, 12%, and 7% lower risk of overall survival, respectively(35).

These findings are particularly relevant in supporting the role of patient-reported outcome assessment as a measure of treatment tolerability. The observation that an early decline in global health status carries prognostic significance suggests that systematic assessment in the immediate postoperative period may also be critical in other disease stages, especially where additional therapies such as immunotherapy or targeted agents are considered(36, 37). Capturing patients' recovery trajectories shortly after surgery could therefore inform readiness to initiate adjuvant treatments and ultimately improve long-term outcomes and possibly identify early patients enable a post treatment rehabilitation/medical optimisation.

Nevertheless, the observation that the GHS decline was the only significant peri-treatment predictor—while other EORTC QLQ-C30 scales did not reach significance—highlights the distinct roles of these metrics. In this clinical setting, the Summary Score may be more sensitive to the acute, transient symptom burden often seen immediately following surgery or radiotherapy(38). In contrast, the GHS appears better suited to capturing a holistic and underlying baseline patient-reported health that can supersede traditional objective prognostic factors, such as performance status or pulmonary function(39). However, given the baseline disparities where SABR patients were older and had higher comorbidity burdens, these results should be viewed as hypothesis-generating. The nature of GHS as a predictor requires further validation in larger, multi-centre cohorts where higher baseline compliance can be ensured to mitigate residual confounding.

While our findings identify an early >10-point decline in GHS at 6 weeks as an independent predictor of lung cancer-specific mortality, we must critically acknowledge the methodological limitations of this observational cohort. As previously reported in the LiLac study(15), compliance with baseline questionnaires was notably higher in the SABR group (78%) compared to the VATS group (54%). This differential attrition and the overall rate of missing baseline data potentially reduce the statistical power of the longitudinal analysis and may introduce selection bias.

This study has some additional potential limitations. It was conducted in a single centre, which may limit generalisability. The sample size was small, reducing the power of subgroup analyses. Patient-reported outcomes were collected at fixed intervals, potentially missing short-term fluctuations or late effects. Finally, baseline differences between the surgery and SABR groups in this context may have influenced outcomes; although preoperative factors were considered, residual confounding cannot be excluded, particularly given the more acute functional impact of surgery.

Conclusions

In conclusion, this study demonstrates that very early changes in patient-reported global health status provide important prognostic information for patients with stage I NSCLC treated with either surgery or SABR. The findings highlight the value of incorporating routine patient-reported outcomes into clinical practice to support risk stratification and shared decision-making. Future research in larger, multi-centre cohorts is needed to validate these observations and to explore strategies for mitigating early declines in quality of life, particularly in the surgical setting.

Conflict of Interest:

CP reports speaker and consultancy honoraria from Astrazeneca, BMS, Roche, Johnson & Johnson, Intuitive. GV reports speakers and consultancy honoraria from Pfizer, Novartis, Eisai, Lilly, Gilead AstraZeneca, Roche, Pfizer, Seagen, Sanofi, Daiichi Sankyo. KF reports participation to advisory boards and/or received fees for speaking for AstraZeneca, Boerhinger-Ingelheim, British-Meyers-Squibb, Lilly and Roche. AB reports personal fees for participating to advisory board meetings with Astra Zeneca, BMS, MSD, Roche, Ethicon, Medtronic. All the other authors have no financial conflicts of interest to declare.

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Supplementary files

S1: CONSORT Flow-chart

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492 **Table 1**: Characteristics of the patients included in the analysis

	Surgery (80 patients)	SABR (62 patients)	p-value
Age	69.4 (8.6)	74.3 (8.9)	0.0004
FEV1%	86.4 (22.6)	78.0 (26.7)	0.015
DLCO%	83.0 (20.4)	71.9 (22.7)	0.002
BMI kg/m^2	26.4 (5.7)	27.3 (5.5)	0.26
sex (male)	37 (46%)	22 (35%)	0.20
CAD	5 (6.3%)	20 (32%)	<0.001
CVD	2 (2.5%)	9 (15%)	0.011
Diabetes	6 (7.5%)	15 (24%)	0.008
PS>1	11 (14%)	37 (60%)	<0.001

493 Results are expressed as averages and standard deviations for numeric variables and
494 count and percentages for categorical ones. FEV1: forced expiratory volume in one
495 second; DLCO: carbon monoxide lung diffusion capacity; BMI: body mass index; CAD:
496 history of coronary artery disease; CVD: history of cerebrovascular disease; PS:
497 performance status.

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Table 2: Results of the competing regression analysis to identify factors associated with lung cancer specific death (competing event: deaths from causes other the lung cancer).

Variables	SHR	p-value	95% CI
Age	0.96	0.26	0.90-1.03
Sex male	0.84	0.75	0.30-2.40
Decline GH >10	5.77	0.019	1.33-25.0
Surgery	0.71	0.65	0.16-3.09
FEV1	0.99	0.46	0.97-1.02
DLCO	0.99	0.96	0.97-1.02
CAD	1.02	0.97	0.32-3.28
CVD	2.77	0.27	0.44-17.2
PS>1	0.50	0.24	0.16-1.59

SHR: Sub distribution hazard ratio; SFEV1: forced expiratory volume in one second; DLCO: carbon monoxide lung diffusion capacity; BMI: body mass index; CAD: history of coronary artery disease; CVD: history of cerebrovascular disease; PS: performance status.GH: Global Health Status

Figures Legend

Figure 1: Kaplan Meier overall survival estimates after surgery or SABR in patients with clinical stage I NSCLC.

Figure 2: Kaplan Meier event free survival estimates after surgery or SABR in patients with clinical stage I NSCLC.

Figure 3: Kaplan Meier lung cancer specific survival estimates after surgery or SABR in patients with clinical stage I NSCLC.

Figure 4: Cumulative incidence of lung cancer deaths in clinical stage I NSCLC patients with and without a large peri-treatment decline in global health status by treatment group.

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Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.