

ORIGINAL ARTICLE

# Video-Assisted Thoracoscopic or Open Lobectomy in Early-Stage Lung Cancer

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## Abstract

**BACKGROUND** There is limited randomized evidence on the comparative outcomes of early-stage lung cancer resection by video-assisted thoracoscopic surgery (VATS) versus open resection.

**METHODS** We conducted a parallel-group multicenter randomized trial that recruited participants with known or suspected early-stage lung cancer and randomly assigned them to open or VATS resection of their lesions. The primary outcome was physical function at 5 weeks as a measure of recovery using the European Organisation for Research and Treatment of Cancer core health-related quality of life questionnaire (QLQ-C30) (scores range from 0 to 100, with higher scores indicating better function; the clinical minimally important difference for improvement is 5 points). We followed the patients for an additional 47 weeks for other outcomes.

**RESULTS** A total of 503 participants were randomly assigned (247 to VATS and 256 to open lobectomy). At 5 weeks, median physical function was 73 in the VATS group and 67 in the open surgery group, with a mean difference of 4.65 points (95% confidence interval, 1.69 to 7.61). Of the participants allocated to VATS, 30.7% had serious adverse events after discharge compared with 37.8% of those allocated to open surgery (risk ratio, 0.81 [95% confidence interval, 0.66 to 1.00]). At 52 weeks, there were no differences in cancer progression-free survival (hazard ratio, 0.74 [0.43 to 1.27]) or overall survival (hazard ratio, 0.67 [0.32 to 1.40]).

**CONCLUSIONS** VATS lobectomy for lung cancer is associated with a better recovery of physical function in the 5 weeks after random assignment compared with open surgery. Long-term oncologic outcomes will require continued follow-up to assess. (Funded by the National

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*\*A complete list of the VIOLET trialists and collaborators is provided in the Supplementary Appendix, available at [evidence.nejm.org](https://evidence.nejm.org).*

## Introduction

**S**urgery is the standard of care for early-stage lung cancer. The use of video-assisted thoracoscopic surgery (VATS) has been increasing worldwide and is currently the most common form of access for lung cancer resection in the United Kingdom.<sup>1</sup> The increased popularity of “minimally invasive” VATS access was based on the assumption that smaller incisions without rib spreading may improve recovery compared with standard open thoracotomy for lung cancer surgery.

Data from randomized controlled trials (RCTs) have been conflicting with regards to any improvements in pain, complications, and overall hospital length of stay,<sup>2,3</sup> and there are no high-quality data on the temporal profile of clinical effectiveness after hospital discharge.

Because research has focused on clinical efficacy, important questions remain, namely whether VATS lobectomy, which is performed through small incisions using extended instruments rather than open thoracotomy conducted with direct visualization and tactile tissue access, would increase procedure-related complications over the postoperative recovery period or lead to suboptimal oncologic outcomes over the longer term.

The Video assisted thoracoscopic lobectomy versus conventional Open LobEcTomy for lung cancer (VIOLET) is a trial, reported in this study, compares VATS with open (thoracotomy) access for intended lobectomy for presumed or diagnosed early-stage lung cancer with the primary outcome of physical function over the first 5 weeks after random assignment; we also evaluated clinical efficacy, safety, and oncologic outcome to 1 year.

## Methods

Full details of the trial have been published<sup>4</sup> and are provided in the protocol and statistical analysis plan, which is available with the full text of this article at [evidence.nejm.org](https://evidence.nejm.org).

## TRIAL DESIGN AND OVERSIGHT

VIOLET is a multicenter parallel-group superiority RCT conducted in nine centers in the United Kingdom. The trial was funded by the National Institute for Health Research (NIHR) and approved by the National Health Service (NHS) Research Ethics Committee (reference number 14/LO/2129). All participants provided written informed consent. Trial oversight was undertaken by The Royal Brompton and Harefield NHS Foundation Trust as sponsor. All authors were responsible for the decision to submit the manuscript for publication; no one else contributed meaningfully to the drafting of the manuscript, other than the copyeditor, who is not listed as an author. There was no confidentiality agreement between the sponsor and the authors or the institutions named to restrict the reporting of the research findings.

## PARTICIPANTS

Eligible patients were 16 years of age or older with suspected or confirmed primary lung cancer (TMN8 staging criteria<sup>5</sup>: primary tumor stage [cT] 1 to 3, regional lymph node involvement stage [cN] 0 to 1, and metastases stage in which the disease was considered suitable for either VATS or open lobectomy) (the inclusion and exclusion criteria<sup>4</sup> are described in full in the Supplementary Appendix, pages 52 and 53). For patients without a confirmed tissue diagnosis, surgeons could perform a confirmatory biopsy or proceed directly to surgery on the basis of a multidisciplinary team recommendation.

## RANDOM ASSIGNMENT AND MASKING

Random assignment took place before the planned surgery to allow operations to be scheduled. Participants were allocated in a 1:1 ratio to VATS or open surgery using a secure Internet-based system (Sealed Envelope Ltd, London, U.K.). Allocation was stratified by center and minimized by surgeon. Clinicians and nurses present during the surgery were aware of the group allocation, but research nurses responsible for outcome data collection and participants were blinded to the group allocation. At the end of the operation, a wound dressing sufficiently large to conceal a thoracotomy incision (regardless of actual access used) was applied.<sup>6</sup> At discharge from hospital, participants were informed of the surgery they had received only after they had been asked to indicate to which group they thought that they had been assigned.

## INTERVENTIONS

Participants in the VATS group underwent a lobectomy with visualization through a telescope and instruments

introduced into one to four keyhole incisions without rib spreading.<sup>4</sup> Participants in the open surgery group underwent a lobectomy through direct vision through a single thoracotomy incision with rib spreading. Rib resection was permitted but not mandated. The type of thoracotomy performed was the surgeon's choice (to be reflective of United Kingdom practice), as was the intraoperative analgesic protocol.

Lymph node dissection was recommended for all participants in line with the International Association for the Study of Lung Cancer guidelines.<sup>7</sup>

When a confirmatory diagnostic biopsy was required before lobectomy (71 cases in the VATS group and 73 cases in the open surgery group), it was undertaken intraoperatively using VATS in all patients. On the basis of the biopsy results, the surgeon would either stop and close or proceed to lobectomy according to the randomly assigned allocation. Patients in whom a lung cancer diagnosis was not confirmed were followed up for the primary outcome at 5 weeks only.

### SURGICAL EXPERTISE

Surgeons were required to have performed at least 40 VATS lobectomies before joining the trial. Open lobectomy is standard in the United Kingdom, and surgical competence in the approach was ensured by specialist registration.

### POSTOPERATIVE CARE

Centers were asked to declare analgesia practices and to standardize analgesic protocol for all participants. Other aspects of postoperative care were carried out in accordance with the center's usual practice.

### OUTCOMES

The primary outcome was physical function as measured by the European Organisation for Research and Treatment of Cancer (EORTC) core health-related quality of life questionnaire (QLQ-C30) at 5 weeks after random assignment. The score ranges from 0 to 100, with higher scores indicating higher function (see sample size and statistical analysis for minimally clinically important difference). Prespecified secondary outcomes included measures of clinical efficacy, oncologic outcomes, safety, and resource use (health economic findings will be reported separately).

Clinical efficacy measures included: pain scores in the first 2 days after surgery; duration of stay in hospital; prolonged incision pain, defined as the need for analgesia more than 5 weeks after random assignment, and quality of life measured using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, QLQ-LC13, and Euro-Qol 5-Dimension 5-Level self-report questionnaires (see Supplementary Appendix, pages 53 and 54 for ranges, interpretation, and minimally important difference where known). Oncologic outcomes included: complete resection during the procedure; upstaging to pN2 disease after the procedure; uptake of adjuvant treatment; and overall and progression-free survival (assessed by computed tomography imaging at 12 months or before as clinically indicated) to 52 weeks.

### SAMPLE SIZE AND STATISTICAL ANALYSIS

In the QLQ-C30, an effect size of 0.2 to 0.6 standard deviations (SD) equates to a clinically important difference in physical function of between 5 and 14 points or approximately a one-category change in performance status.<sup>8</sup> We calculated that a sample size of 498 participants would be sufficient for the study to have 90% power to detect a difference of 0.25 SD using a two-sided test, at a 5% level of significance, assuming a correlation between pre- and postsurgery measures of 0.3 and between postsurgery repeated measures of 0.6, and allowing for up to a 20% dropout. The trial also had 80% power to detect a 1-day difference in duration of stay in hospital (i.e., median 3 versus 4 days), assuming a 2% in-hospital mortality rate.<sup>4</sup> Analyses were performed on an intention-to-treat basis.

The primary outcome and other longitudinal quality-of-life outcomes were analyzed using joint longitudinal survival models, with results presented as mean differences and 95% confidence intervals (CIs) unless otherwise noted. If this model was a poor fit for the data, alternative models were explored (see details in Supplementary Appendix, pages 55 and 56). Length of hospital stay and survival were analyzed using Cox proportional hazards regression.

Generalized linear models were used for binary outcomes and generalized structural equation models for multinomial outcomes. Effect estimates are presented as risk ratios and 95% CIs.

Analyses were adjusted for center and surgeon where possible, fitted as random effects (or as stratification variables in

time-to-event analyses). Longitudinal outcomes were adjusted for baseline preoperative score fitted as a fixed effect.

A prespecified sensitivity analysis for the primary outcome excluded participants with benign disease. From the data received from each patient concerning group assignment before revealing this information to them, we calculated the Bang Blinding Index.

Multiple imputation was used to account for missing data. Adjustments for multiplicity for quality-of-life outcomes were performed using the method of Benjamini and Hochberg<sup>9</sup>; however, no multiplicity adjustments for the other secondary and exploratory end points were defined (therefore, only point estimates and 95% CIs are provided). The CIs have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects. Open surgery was the reference group in all analyses. All statistical analyses were performed using Stata, version 16.1 (StataCorp, College Station, TX).

## Results

### PATIENTS AND TREATMENT

Of the 2109 patients from nine sites screened for eligibility between July 2015 and February 2019, a total of 503 were randomly assigned, 247 to VATS and 256 to open lobectomy. One participant withdrew after random assignment; therefore, the analysis population consisted of 502 participants. The participant flow diagram is illustrated in [Figure 1](#). Reasons for ineligibility and nonconsent, protocol deviations, and withdrawals after random assignment are presented in Tables S1 to S3 in the Supplementary Appendix. The median follow-up was 12.1 months (interquartile range, 11.6 to 12.6).

The baseline characteristics were balanced between the two groups ([Table 1](#) and Table S4). The mean age of our participants was 69 (SD 8.8) years, and 249 (49.5%) were men, with the majority of our trial population presenting with a tumor measuring 3 cm or less (cT1a to 1c; 338 of 502, 67.3%) and no lymph node involvement (cN0; 470 of 502, 93.6%).

In total, 453 of 502 participants (90.2%) underwent lobectomy performed by 1 of 25 surgeons, and 436 (96.2%) received their allocated treatment ([Fig. 1](#) and [Table 1](#)). Of the

453 participants who underwent lobectomy, primary lung cancer was confirmed in 444 (98.0%). The rib-spreading protocol was adhered to in all cases, and no participants allocated to VATS received more than four ports ([Table 1](#)). The overall in-hospital mortality rate was 1.4% (7 of 502) and 1.5% (7 of 453; 2 of 221 for VATS and 5 of 232 for open lobectomy) for participants who underwent lobectomy.

Of the participants allocated to VATS, 15 underwent open surgery (15 of 247, 6.1%); 1 patient decided preoperatively to have open surgery, and the remaining 14 conversions were initiated by the surgeon intraoperatively, giving a rate of 14 of 246 (5.7%). The main reasons for conversion from VATS to open surgery were adhesions and bleeding (Table S6). Of the participants allocated to open surgery, two underwent VATS surgery (2 of 256, 0.8%). Both participants withdrew from the randomized intervention and opted for VATS.

### RECOVERY FROM SURGERY — PHYSICAL FUNCTION (PRIMARY OUTCOME)

Using physical function as the global measure of recovery, participants allocated to VATS had significantly better physical functioning at 5 weeks, with a median score of 73 versus 67 in the open surgery group (mean difference, 4.65 [95% CI, 1.69 to 7.61];  $P=0.009$ ) (Table S7). The improvement in physical function was more marked in the early discharge period; from the 6-month observation point out to 1 year, the groups were similar in this measure ([Fig. 2](#)). The sensitivity analysis, excluding participants with benign disease, was consistent with the primary analysis (Table S8).

### SECONDARY OUTCOMES

#### Clinical Efficacy

Participant-reported pain on postoperative day 1 was similar in the two groups; on day 2, it was 3 (1 to 5) (median and interquartile range) in the VATS group compared with 4 (2 to 5) in the open surgery group (mean difference,  $-0.54$  points [95% CI,  $-0.99$  to  $-0.09$ ]) ([Table 2](#), [Fig. 3A](#), and Table S9). Analgesic consumption during the postoperative period in hospital in the two groups had a mean ratio (VATS/open) of 0.90 [95% CI, 0.80 to 1.01] and is shown in [Figure 3B](#) and Table S10. Prolonged incisional pain was experienced by 59.6% of the participants in the VATS group and by 72.3% of the participants in the open surgery group (mean difference of  $-12.7$  [95% CI,  $-21.1$

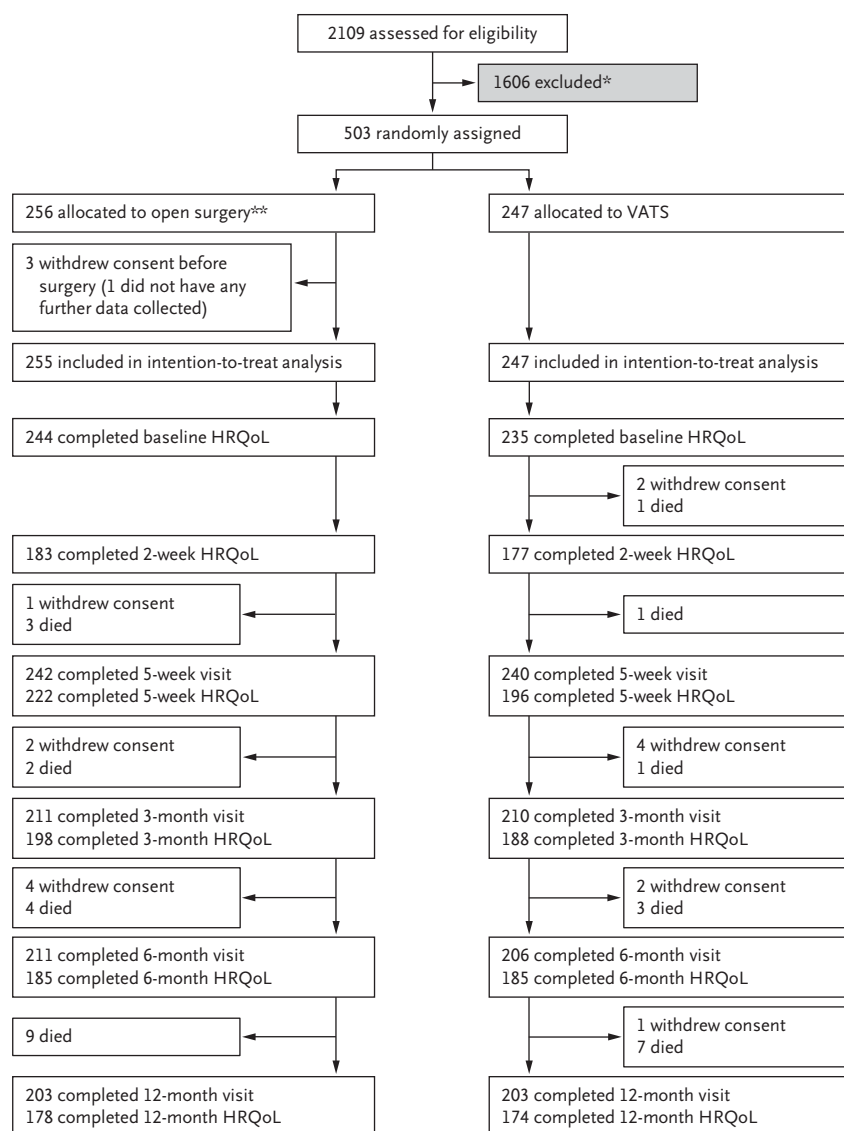


Figure 1. Participant Flow through the Trial.

\*Reasons for patients being excluded before random assignment are detailed in Table S1. \*\*Patients were converted to VATS from the open surgery randomly assigned group because of a change in operative plan decided by the surgeon and patient immediately prior to surgery. See Table S2, Protocol deviations, for data. HRQoL denotes health-related quality of life and VATS video-assisted thoracoscopic surgery.

to −4.0] percentage points; risk ratio, 0.82 [95% CI, 0.72 to 0.94]) (Table S13). Pain scores measured using the QLQ-C30 and QLQ-LC13 showed similar trends up to 1 year; these scores and other related outcome measures are shown in Tables S13 to S17.

The median length of hospital stay was 4 days for the VATS and 5 days for the open surgery group, corresponding to a 34% higher probability of discharge on any given

day for patients randomly assigned to VATS (hazard ratio, 1.34 [95% CI, 1.09 to 1.65]) (Fig. 4).

To assess the success of masking group assignment, patients were asked to which group they believed they had been assigned; this was carried out before their actual group assignment was revealed to them. On the day of discharge, 107 out of 209 patients (51.2%) and 95 out of 208 patients (45.74%) correctly guessed their group



| Table 1. Baseline Clinical Characteristics and Surgical Details* |                                   |   |                |
|--|-----------------------------------|---|----------------|
| Characteristics and Details                                      | Randomly Assigned to VATS (n=247) | Randomly Assigned to Open Surgery (n=255) | Total (n=502)  |
| Characteristics  |                                   |   |                |
| Age (yr)   | 69 (8.7)                          | 69 (9.0)                                  | 69 (8.8)       |
| Male   | 119/247 (48.2)                    | 130/255 (51.0)                            | 249/502 (49.6) |
| Clinical stage   |                                   |   |                |
| cT   |                                   |   |                |
| 1a   | 24/247 (9.7)                      | 17/255 (6.7)                              | 41/502 (8.2)   |
| 1b   | 77/247 (31.2)                     | 86/255 (33.7)                             | 163/502 (32.5) |
| 1c   | 64/247 (25.9)                     | 70/255 (27.5)                             | 134/502 (26.7) |
| 2a   | 50/247 (20.2)                     | 47/255 (18.4)                             | 97/502 (19.3)  |
| 2b   | 13/247 (5.3)                      | 16/255 (6.3)                              | 29/502 (5.8)   |
| 3  | 19/247 (7.7)                      | 19/255 (7.5)                              | 38/502 (7.6)   |
| cN   |                                   |   |                |
| 0  | 232/247 (93.9)                    | 238/255 (93.3)                            | 470/502 (93.6) |
| 1  | 15/247 (6.1)                      | 17/255 (6.7)                              | 32/502 (6.4)   |
| ECOG status  |                                   |   |                |
| 0  | 148/244 (60.7)                    | 172/252 (68.3)                            | 320/496 (64.5) |
| 1  | 84/244 (34.4)                     | 75/252 (29.8)                             | 159/496 (32.1) |
| 2  | 10/244 (4.1)                      | 5/252 (2.0)                               | 15/496 (3.0)   |
| 3  | 2/244 (0.8)                       | 0/252 (0.0)                               | 2/496 (0.4)    |
| Mean predicted lung function (%)                                 |                                   |   |                |
| FEV <sub>1</sub> †   | 82 (19.8)                         | 82 (21.2)                                 | 82 (20.5)      |
| FVC‡   | 95 (17.1)                         | 95 (18.3)                                 | 95 (17.7)      |
| Tlco§  | 76 (26.3)                         | 72 (20.4)                                 | 74 (23.5)      |
| Surgical details   |                                   |   |                |
| Operative time (h)¶  | 2.5 (2.0–3.1)                     | 2.2 (1.8–2.8)                             | 2.4 (1.9–2.9)  |
| Lobectomy performed  | 221/247 (89.5)                    | 232/255 (91.0)                            | 453/502 (90.2) |
| VATS performed   | 206/221 (93.2)                    | 2/232 (0.9)                               | 208/453 (45.9) |
| No. of VATS ports  |                                   |   |                |
| One port   | 42/206 (20.4)                     | 0/2 (0.0)                                 | 42/208 (20.2)  |
| Two ports  | 18/206 (8.7)                      | 0/2 (0.0)                                 | 18/208 (8.7)   |
| Three ports  | 119/206 (57.8)                    | 1/2 (50.0)                                | 120/208 (57.7) |
| Four ports   | 27/206 (13.1)                     | 1/2 (50.0)                                | 28/208 (13.5)  |
| Thoracotomy performed  | 15/221 (6.8)                      | 230/232 (99.1)                            | 245/453 (54.1) |
| Posterolateral thoracotomy                                       | 12/15 (80.0)                      | 161/230 (70.0)                            | 173/245 (70.6) |
| Anterior thoracotomy   | 3/15 (20.0)                       | 69/230 (30.0)                             | 72/245 (29.4)  |

\* Data are presented as median (interquartile range), mean (SD), or n/N (%). For further information on the participant population, see Table S4. cN denotes regional lymph nodes, cT primary tumor, ECOG Eastern Cooperative Oncology Group (status 0 = fully active, able to carry on all predisease performance without restriction; 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature [e.g., light housework or office work]; 2 = ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours; 3 = capable of only limited self-care, confined to bed or chair more than 50% of waking hours), FEV<sub>1</sub> forced expiratory volume in 1 second, FVC forced vital capacity, Tlco transfer capacity of the lung, and VATS video-assisted thoracoscopic surgery.

† 12 patients had missing data (VATS 7, open 5).

‡ 15 patients had missing data (VATS 8, open 7).

§ 118 patients had missing data (VATS 60, open 58).

¶ 2 patients had missing data (VATS 1, open 1).

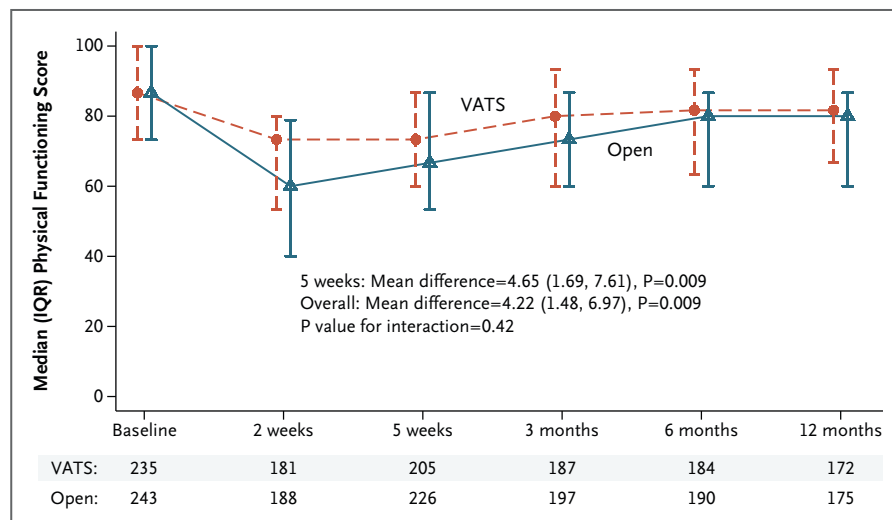


Figure 2. Primary Outcome Measure — QLQ-C30 Physical Functioning.

Circles and triangles denote the median values in the two groups, and bars depict the interquartile range (IQR). Numbers of observations are shown at the bottom of the figure. Estimates are the mean difference in score with a 95% confidence interval, estimated from the regression model fitted to the data. The primary outcome is the score at 5 weeks. The overall mean difference is estimated over 1 year. QLQ-C30 denotes European Organisation for Research and Treatment of Cancer core health-related quality of life questionnaire, VATS video-assisted thoracoscopic surgery.

assignment in the VATS and open surgery groups, respectively. A score of 50% would be expected by chance alone.

### Safety

Summaries and treatment effects for safety outcomes by group are described in [Table 2](#) and Tables S20 to S23 and Figs. S26 and S27. The proportion experiencing adverse events in hospital was 81 of 247 (33%) in the VATS group and 113 of 255 (44%) in the open surgery group (risk ratio, 0.74 [95% CI, 0.66 to 0.84]), a difference driven mainly by infective and renal complications, as shown in Table S20 and Figure S26. The outcome of persistent air leak, defined as discharge with a drain, was added partway through the study and therefore only collected for 281 patients (56% of total participants). Air leaks occurred in 20 of 135 patients (15%) in the VATS group and in 11 of 146 patients (8%) in the open surgery group.

There was no difference in serious adverse events (SAEs) in hospital (risk ratio, 0.98 [95% CI, 0.59 to 1.63]) ([Table 2](#) and Table S20). Bleeding as a result of vascular injury that prolonged the hospital stay occurred in 4.7% of participants in the VATS group (6 of 129) compared with 0.8% (1 of 127) in the open surgery group, but none resulted in death (Tables S20 and S21).

After discharge, 75 of 244 patients randomly assigned to VATS (30.7%) had SAEs compared with 94 of 249 (37.8%) in the open surgery group (risk ratio, 0.81 [95% CI, 0.66 to 1.00]) ([Table 2](#), Table S22, and Fig. S27). Readmission rates were 70 of 241 (29.0%) in the VATS group versus 88 of 245 (35.9%) in the open surgery group (Table S23). Reasons for readmission to hospital and death are described in [Table 2](#) and Table S23.

### Oncologic Outcomes

The median number of lymph node stations harvested was five in both groups, with a median of three mediastinal nodes harvested. Complete pathologic (R0) resection, upstaging from cN0 to pN1, and upstaging from cN0/1 to pN2 were similar in the two groups ([Table 2](#)).

Of those eligible by stage criteria for chemotherapy, 28 of 55 (50.9%) in the VATS group and 28 of 61 (45.9%) in the open surgery group received adjuvant treatment. There was no difference in the time to uptake of adjuvant chemotherapy (hazard ratio, 1.12 [95% CI, 0.62 to 2.02]) (Table S13 and Figs. S28 and S29).

There was no difference in the proportion identified with recurrence/progression of lung cancer on clinical follow-up and CT at a median follow-up of 12 months, which was

Table 2. Oncologic, Efficacy, and Safety Outcomes\*

| Outcome  | Randomly Assigned to VATS<br>(n=247) | Randomly Assigned to Open<br>Surgery (n=255) | Effect (95% CI)   |
|--|--------------------------------------|--|---|
| Efficacy outcomes                                  |                                      |  |   |
| VAS pain score                                     |                                      |  |   |
| Baseline‡  | 0 (0.0–1.0)                          | 0 (0.0–1.0)                                  |   |
| Day 1§   | 4 (2.0–5.0)                          | 4 (2.0–5.0)                                  | MDiff, –0.024 (–0.463 to 0.414)                                 |
| Day 2¶   | 3 (1.0–5.0)                          | 4 (2.0–5.0)                                  | MDiff, –0.539 (–0.986 to –0.092)                                |
| Length of hospital stay (d)                        | 4 (3–7)                              | 5 (3–8)                                      | Hazard ratio, 1.34 (1.09–1.65)                                  |
| Oncologic outcomes                                 |                                      |  |   |
| Total No. of lymph node stations harvested         | 5 (4.0–6.0)                          | 5 (4.0–6.0)                                  |   |
| Mediastinal nodes harvested (stations 2–9)         | 3 (3.0–4.0)                          | 3 (3.0–4.0)                                  |   |
| Complete (R0) resection                            | 210/215 (97.7)                       | 219/224 (97.8)                               | Risk ratio, 0.999 (0.973–1.026)<br>RD, –0.0009 (–0.03 to 0.025) |
| Site of residual (R1) disease                      |                                      |  |   |
| Bronchial margin                                   | 2/5 (40)                             | 3/5 (60)                                     |   |
| Vascular margin                                    | 0/5 (0)                              | 1/5 (20)                                     |   |
| Lung parenchymal margin                            | 2/5 (40)                             | 0/5 (0)                                      |   |
| Other  | 1/5 (20)                             | 0/5 (0)                                      |   |
| No data  | 0/5 (0)                              | 1/5 (20)                                     |   |
| Locoregional recurrence                            |                                      |  |   |
| Lung   | 3/3 (16.7)                           | 7/6 (28.6)                                   |   |
| Mediastinal  | 4/4 (22.2)                           | 1/1 (4.8)                                    |   |
| Bronchus   | 0                                    | 1/1 (4.8)                                    |   |
| Pleura and lymph nodes                             | 1/1 (5.6)                            | 0  |   |
| Not collected†                                     | 3/2 (11.1)                           | 4/4 (19)                                     |   |
| Safety outcomes                                    |                                      |  |   |
| Any in-hospital adverse event                      | 81/247 (32.8)                        | 113/255 (44.3)                               | Risk ratio, 0.74 (0.66–0.84)<br>RD, –11.5 (–16.2 to –6.8)       |
| Any in-hospital SAE                                | 20/247 (8.1)                         | 21/255 (8.2)                                 | Risk ratio, 0.98 (0.59–1.63)<br>RD, –0.1 (–4.3 to 4.0)          |
| Postdischarge SAEs (events/patients)               | 142/75 (30.7)                        | 207/94 (37.8)                                | Risk ratio, 0.81 (0.66–1.00)<br>RD, –7.0 (–14.0 to –0.05)       |
| In-hospital adverse events                         |                                      |  |   |
| Cardiac disorders                                  | 24/247 (9.7)                         | 24/255 (9.4)                                 |   |
| Infections and infestations                        | 40/247 (16.2)                        | 71/255 (27.8)                                |   |
| Respiratory, thoracic, and mediastinal disorders   | 18/247 (7.3)                         | 21/255 (8.2)                                 |   |
| Postdischarge SAEs                                 |                                      |  |   |
| Gastrointestinal disorders                         | 9/7 (2.9)                            | 27/16 (6.4)                                  |   |
| General disorders                                  | 12/12 (4.9)                          | 14/12 (4.8)                                  |   |
| Infections and infestations                        | 51/35 (14.3)                         | 48/37 (14.9)                                 |   |
| Respiratory, thoracic, and mediastinal disorders   | 25/22 (9.0)                          | 39/27 (10.8)                                 |   |
| Surgical and medical procedures                    | 12/11 (4.5)                          | 25/19 (7.6)                                  |   |
| Deaths following discharge from hospital to 1 year | 11/244 (4.5)                         | 13/249 (5.2)                                 |   |

(continued)



Table 2. Oncologic, Efficacy, and Safety Outcomes\* (cont.)

| Outcome             | Randomly Assigned to VATS<br>(n=247) | Randomly Assigned to Open<br>Surgery (n=255) | Effect (95% CI) |
|---------------------|--------------------------------------|--|-----------------|
| Causes of death     |                                      |  |                 |
| Disease progression | 7/11 (63.6)                          | 5/13 (38.5)                                  |                 |
| Pneumonia           | 2/11 (18.2)                          | 0/13 (0)                                     |                 |

\* Data are presented as median (interquartile range), events/patients (%), or n/N (%) unless otherwise indicated. Analyses are adjusted for operating surgeon and center. CI denotes confidence interval, MDiff mean difference, R0 resection no residual tumor, R1 resection microscopic residual tumor, RD risk difference, SAE serious adverse event, VAS visual analog scale (range 0 to 10; higher scores indicate more pain), and VATS video-assisted thoracoscopic surgery.

† Data are recurrences/patients (%). Data collection was added partway through the study, so data are only available for a subset of participants. Participants could have multiple recurrence types, so denominator will not sum to the total No. of participants.

‡ 19 patients had missing data (VATS 10, open 9); 100 imputed datasets were used.

§ 20 patients had missing data (VATS 11, open 9); 100 imputed datasets were used.

¶ 45 patients had missing data (VATS 22, open 23); 100 imputed datasets were used.

7.7% (16 of 207) in the VATS group and 8.2% (17 of 208) in the open surgery group. Locations of recurrence are summarized in Table S24. The hazard ratio for progression-free survival for VATS compared with open surgery was 0.74 (95% CI, 0.43 to 1.27) (Table S12 and Fig. S30). By 1 year, 13 of 226 participants (5.8%) in the VATS group and 18 of 228 participants (7.9%) in the open surgery group had died. The hazard ratio for overall survival comparing VATS with open surgery was 0.67 (95% CI, 0.32 to 1.40) (Table S13 and Fig. S31). Other aspects of quality of life are reported in Tables S14 to S19 and Figures S1 to S25.

## Discussion

Our results suggest that VATS lobectomy results in better physical function at 5 weeks, shorter postoperative hospital stay despite more air leaks and bleeding, fewer SAEs after discharge and readmissions, and less pain. Prior to 2010, there was little uptake of VATS for lung cancer surgery in the United Kingdom,<sup>10</sup> but in less than a decade (by 2017), exponential growth in popularity led it to become the most common access for lung cancer resection,<sup>1</sup> largely on its own momentum on the promise of “better recovery,” unsupported by any robust clinical trial evaluation.

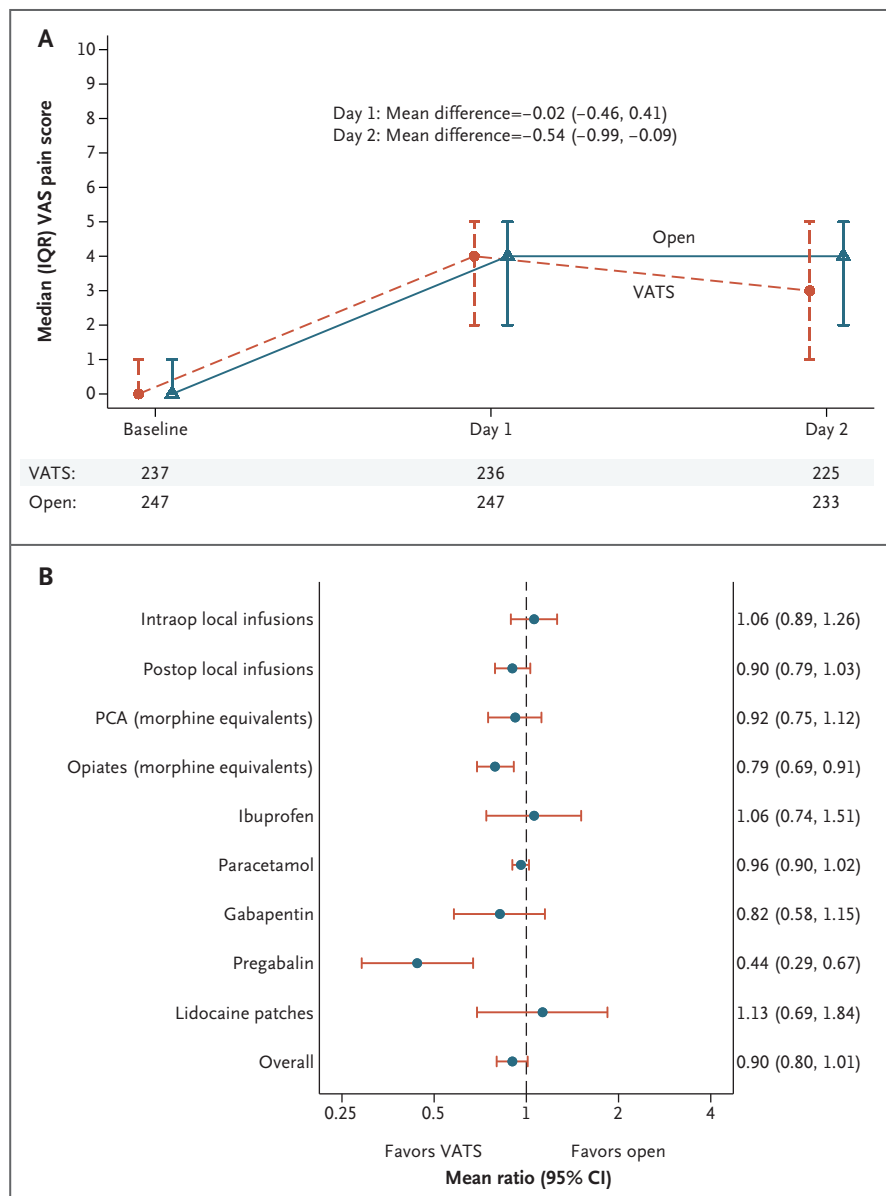
Higher-quality but conflicting evidence emerged in 2016, with Bendixen et al.<sup>2</sup> reporting the principal benefits of VATS access as lower moderate to severe postoperative pain and shorter length of stay and in 2018, when Long et al.<sup>3</sup> reported no difference in length of stay or any other clinical outcomes (this trial did not report pain as an outcome).

## CLINICAL EFFICACY

We chose physical function as our primary global measure of recovery at 5 weeks and observed a statistically significant improvement of 4.65 units, albeit one that did not achieve the 5-unit improvement that has been offered as a “minimally important difference.”<sup>7</sup> However, the concept of a clinically minimally important difference in performance status is difficult to quantify, and our finding that many, but not all, secondary outcomes showed patient-facing benefit over the year of observation is consistent with the idea that VATS provided benefit with respect to patient comfort, compared with open surgery. Additional data that support this point of view are our longitudinal analyses that suggest that patients in the open thoracotomy group achieved function similar to that achieved, on average, in the VATS group in 5 weeks only after 6 months of recuperation.

Pain is a confounding factor to consider in studies such as this, because pain scores are modified by the amount of analgesics administered. To control for this, we standardized total opiate usage in morphine equivalents and performed adjusted analyses of raw pain scores with respect to total amount of analgesia consumed. Patients randomly assigned to VATS experienced less in-hospital pain with less analgesic consumption. The duration of benefit was sustained on all pain-related quality-of-life subscales (including overall pain, chest pain, and incision pain) documented up to 1 year.

Our trial was a pragmatic trial to ascertain the impact of VATS versus open surgery in as close to a real-world (United Kingdom surgical practice) setting as possible. Although the type of open thoracotomy used by a given surgeon has the potential to influence pain, we did not mandate the type of thoracotomy performed (therefore,



**Figure 3. In-Hospital Pain Scores and Analgesic Mean Ratios.**

(A) Chart shows visual analog scale (VAS) pain scores over time. Circles and triangles denote the median values in the two groups, and bars depict the interquartile range (IQR). Numbers of observations are shown at the bottom of the figure. Estimates are the mean difference in VAS score with a 95% confidence interval (CI), estimated from the regression model fitted to the data. (B) Chart shows analgesic mean ratios. Circles denote the mean ratios, and bars depict the 95% CI, estimated with bootstrapping. Intraop denotes intraoperative, PCA patient-controlled analgesia, Postop postoperative, and VATS video-assisted thoracoscopic surgery.

our results are representative of United Kingdom surgical practice, in which the posterolateral thoracotomy is standard). In addition, we wanted to compare VATS surgery (without mandating exactly how the surgery was to be performed) with the access and techniques with which our surgeons had the most experience.

## SAFETY

Our results suggest that lobectomy for cancer could be performed by VATS with the same operative quality standards of a cancer operation performed through open thoracotomy. There was more bleeding and there were more patients with air leaks in the VATS group, but these events

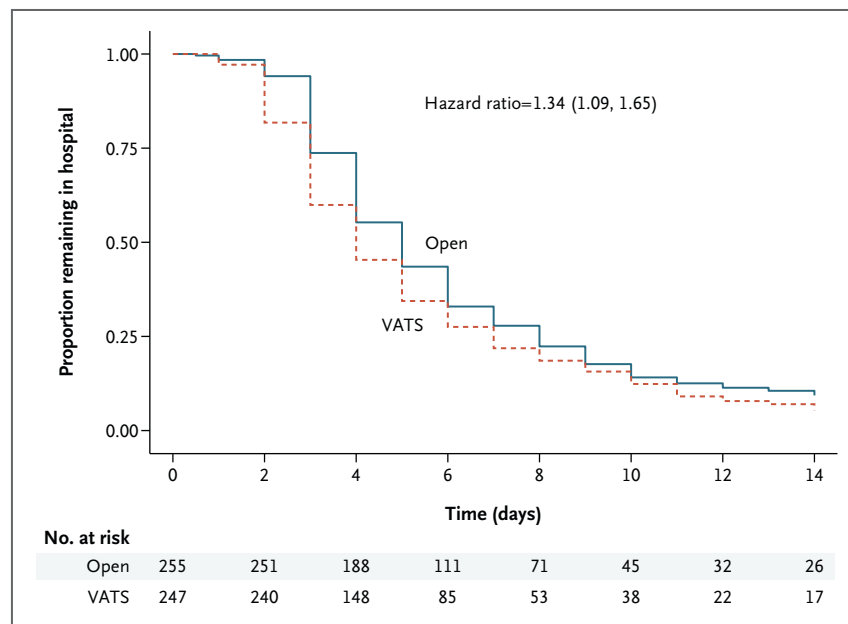


Figure 4. Length of In-Hospital Stay.

Graph shows Kaplan-Meier estimates of the length of hospital stay from surgery to discharge in days. Numbers of participants in hospital on each day are shown at the bottom of the figure. HR denotes hazard ratio, VATS video-assisted thoracoscopic surgery.

did not have a major impact on patient outcomes. Although better physical function and overall quality of life was enjoyed by patients randomly assigned to VATS, this did not translate to a shorter time to adjuvant chemotherapy or any improvement in compliance with adjuvant treatment as reported previously.<sup>11</sup> It is reassuring that our data for overall and disease-free survival are quite similar, even perhaps favoring VATS lobectomy. Although data from nonrandomized studies indicated a possible survival advantage with VATS lobectomy, our trial (nor any individual trial published to date) was not powered to detect any difference in survival, and hence, we are not able to make any inferences on longer-term cancer control or mortality.

## LIMITATIONS

A limitation that is common to most surgical trials is the inability to blind the participants when an incision is performed. While we applied dressings in the in-hospital period, they were removed on discharge so the participant could see (and was allowed to ask about directly) the type of incision received. Our trial design specified a minimum expertise for VATS; we did not specify similarly for open surgery. During the time frame of our study (2016 to 2019), the standard of training of participating thoracic

surgeons in the United Kingdom was based on open thoracotomy access. At no stage would it be the case that surgeons of this cohort would be trained preferentially by VATS. Given the wealth of thoracotomy experience of our surgeons, bias against thoracotomy experience is very unlikely. We did not formally risk stratify our patients, as case selection for surgery took place before random assignment, but because the comorbidities (many of which are used in the estimation of risk) are balanced because of random assignment, imbalance in risk profile is unlikely.

## Conclusion

Surgery for early-stage lung cancer performed through VATS access was associated with less pain, more air leaks, and bleeding but overall fewer in-hospital complications, leading to shorter length of stay without any compromise to oncologic resection compared with open thoracotomy. The benefits of minimal access surgery extended after discharge, with superior physical function, continued less pain, fewer SAEs and hospital readmissions, and improved general quality of life at 1 year must be balanced against the long-term oncologic outcomes, which cannot be determined at this time.

## Disclosures

Author disclosures and other supplementary materials are available at [evidence.nejm.org](https://evidence.nejm.org).

A data sharing statement provided by the authors is available at [evidence.nejm.org](https://evidence.nejm.org).

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