

Impact of video-assisted thoracoscopic lobectomy versus open lobectomy for lung cancer on recovery assessed using self-reported physical function: VIOLET RCT

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Scientific summary

The VIOLET RCT

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Scientific summary

Introduction

Lung cancer is a leading cause of cancer death. In early-stage lung cancer, surgery is commonly undertaken through an open thoracotomy. Since minimal access video-assisted thoracoscopic surgery (VATS) was introduced, the technique has evolved and has been applied in lung cancer resections on the premise that smaller incisions without rib spreading may allow for quicker recovery. Most evidence for VATS is from non-randomised studies or randomised trials that are not directly applicable to UK practice.

Objectives

To compare the clinical effectiveness and cost-effectiveness of VATS lobectomy with open surgery for the treatment of lung cancer.

Methods

Study design

A multicentre, superiority, parallel-group randomised controlled trial with an integrated QuinteT Recruitment Intervention and blinding.

Settings and participants

Nine NHS hospitals with an accredited lung cancer multidisciplinary team and surgeon(s) were eligible to take part. Surgeons were eligible if they had performed at least 40 VATS lobectomies. Lobectomy via open surgery is standard, and competence is assured by specialist registration.

Patients aged ≥ 16 years with suspected or confirmed primary lung cancer [i.e. clinical tumour stage 1–3 (cT1–3), node stage 0–1 (N0–1) or metastasis stage 0 (M0)] whose disease was considered suitable for both surgeries were eligible.

Royal Brompton Hospital (London, UK) and Harefield Hospital (Uxbridge, UK) sponsored the trial, which was approved by the Research Ethics Committee London–Dulwich (reference 14/LO/2129).

Interventions

Video-assisted thoracoscopic surgery lobectomy was undertaken through one to four keyhole incisions without rib spreading. Open surgery used a single incision, rib spreading and optional rib resection. Operations were carried out under general anaesthesia and with patients in the lateral decubitus position.

Randomisation and blinding

Participants were randomised 1 : 1 to VATS or open surgery using a secure internet-based randomisation system, with cohort minimisation to ensure balance across groups by surgeon and site. Randomisation was performed within 1 week of surgery once eligibility had been confirmed and consent given.

Outcome assessors were blinded throughout and participants were blinded until hospital discharge. Blinding was achieved by applying adhesive dressings so that they were positioned to cover both real and potential incision/port locations. Dressings were applied in the operating room and changed after 3 days by a nurse not involved in data collection. Participants were asked to turn their head away while actual and potential wounds were being cleaned and dressed.

Follow-up

Participants were followed up at discharge and at 2 weeks, 5 weeks, 3 months, 6 months and 12 months post randomisation. Participants attended hospital at 5 weeks and 12 months. Other follow-ups were via telephone.

Outcomes

The primary outcome was patient-reported physical function, which was measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) at 5 weeks. Secondary outcomes were complete resection, upstaging to pathologic node stage 2 (pN2) disease, time from surgery to hospital discharge, pain in the first 2 days, adverse health events, uptake of adjuvant treatment, overall and disease-free survival, incision pain requiring analgesia for > 5 weeks post randomisation, quality of life at each follow-up [assessed using the EORTC QLQ-C30, Quality of Life Questionnaire Lung Cancer 13 (QLQ-LC13) and EQ-5D-5L questionnaires] and resource use to 1 year.

Sample size

Physical function at 5 weeks was hypothesised to be superior with VATS lobectomy. The target effect size was 0.25 standard deviations (SDs). Conservative estimates of the correlations between repeated measures were used (0.3 between pre and post measures and 0.6 between repeated post measures). The sample size was 498 participants, which provided 90% power at the 5% significance level, allowing for 20% dropout.

QuinteT Recruitment Intervention

The QuinteT Recruitment Intervention involved identifying and addressing challenges and training recruiters to deal with potential difficulties. Recruitment issues were identified through staff interviews, audio-recordings of recruitment discussions, review of screening/eligibility information, charting patient pathways and observing study meetings. Collaboratively developed strategies to address issues were disseminated through group and individual feedback to recruiters, tips documents, meetings and newsletters.

Statistical analyses

Data were analysed by intention to treat. The analysis population was all randomised participants, excluding patients who had withdrawn and were unwilling for their data to be used.

The model used to compare longitudinal outcomes was dependent on model fit, with a joint longitudinal-survival model being the preferred choice. Time-by-treatment interactions were included and overall treatment effects are presented unless the interaction reached 10% statistical significance, when effects for each time point are reported. The primary outcome was estimated from a model with a time-by-treatment interaction. Time-to-event outcomes were compared using Cox proportional hazards regression. Binary and multinomial outcomes were analysed using generalised linear and structural equation models, respectively. Model assumptions and fit were assessed graphically.

Open surgery was the reference group. Analyses were adjusted for centre, surgeon and baseline preoperative score, where measured. Subgroup effects were estimated by adding a treatment-by-subgroup interaction term into the model. Sensitivity analysis of the primary outcome, excluding participants with benign disease, and exploratory analysis of pain scores by number of incisions were prespecified.

For QLQ-C30 and QLQ-LC13 outcomes, missing data were imputed, results were combined using Rubin's rules and significance levels were adjusted for multiplicity. Analyses were performed using Stata® version 16.1 (StataCorp LP, College Station, TX, USA).

Economic evaluation

The within-trial economic evaluation used the perspective of the NHS and Personal Social Services. The primary outcome was quality-adjusted life-years (QALYs), estimated using the EQ-5D-5L. Resource use was costed using published reference costs. The area under the curve was used to calculate the QALYs accrued by each participant.

Missing data were imputed and QALYs between groups were adjusted for baseline EQ-5D-5L utility. Bootstrapping was used to quantify uncertainty in costs and outcomes. Sensitivity analyses were used to investigate the impact of varying unit costs for key cost drivers, high-cost participants and not adjusting for baseline utility. Analyses were conducted in Stata version 15 and Microsoft Excel® 2016 (Microsoft Corporation, Redmond, WA, USA).

Results

Patient screening and recruitment

Between July 2015 and February 2019, 2109 patients were assessed for eligibility, of whom 503 (50% of eligible patients and 59% of patients approached) were recruited and randomised (VATS, $n = 247$; open surgery, $n = 256$). Recruitment exceeded target throughout.

Withdrawals

Nineteen participants withdrew (three participants before surgery and 16 participants after surgery). The most cited reason was 'participant changed their mind'.

Protocol deviations

There were 66 deviations. Forty-nine patients did not undergo a lobectomy. In addition, 17 patients crossed over: 15 patients randomised to VATS received open surgery (participant choice, $n = 1$; intraoperative conversions, $n = 14$) and two patients randomised to open surgery had VATS (participant choice, $n = 2$). The primary reason for not undergoing lobectomy was benign disease on frozen section. The most common reasons for conversion from VATS to open surgery were diffuse pleural adhesion ($n = 4$) and bleeding from vascular injury ($n = 4$).

Patient follow-up

Follow-up data at 1 year were available for 81% of participants.

Numbers analysed

The analysis population comprised 502 randomised participants.

Baseline data and operative characteristics

Baseline characteristics were similar in the two groups. The mean age of participants was 69 (SD 8.8) years, and 249 (49.5%) participants were men. Most participants were white (96.4%) and past or current smokers (87.3%). Most participants were cT stage 1 (67.2%) and cN stage 0 (95.6%). A total of 242 participants did not have a tissue-confirmed diagnosis and underwent a biopsy first, 32 (13.2%) of whom had confirmed benign disease. All surgeons adhered to the surgical protocol.

QuinteT Recruitment Intervention

Examples of good practice (e.g. expressing uncertainty) and recruitment challenges (e.g. recruiters using imbalanced/loaded terminology to explain the operations) were identified. Feedback was aimed at addressing challenges by providing tips on optimising recruitment consultations. There were noticeable improvements after feedback, although the precise impact of the feedback is difficult to discern because of the many contributing factors.

Primary outcome: QLQ-C30 physical function at 5 weeks

Participants allocated to VATS had a median score of 73 [interquartile range (IQR) 60.0–86.7], compared with a median score of 67 (53.3–86.7) for participants allocated to open surgery [mean difference (MD) (VATS – open surgery) 4.65, 95% confidence interval (CI) 1.69 to 7.61; $p = 0.0089$], indicating better physical function in the VATS group. Excluding participants with benign disease gave consistent results.

Secondary outcomes**Complete resection**

The median number of lymph node stations and mediastinal nodes harvested was 5 (IQR 4–6) and 3 (IQR 3–4), respectively, in both groups. Complete R(0) resection was achieved in 429 of 439 (97.7%) participants (relative risk 0.999, 95% CI 0.97 to 1.26; $p = 0.94$). Those participants with residual disease had R1 disease.

Lymph node upstaging

Upstaging from clinical node stage 0 (cN0) to pathologic node stage 1 (pN1) and from clinical node stage 0 or 1 (cN0/1) to pN2 was similar in both groups (relative risk 1.18, 95% CI 0.54 to 2.58; $p = 0.68$ and relative risk 1.31 95% CI 0.60 to 2.86; $p = 0.50$, respectively).

Pain in the first 2 days post surgery

Pain scores were similar in the two groups on day 1 (median 4, MD –0.02, 95% CI –0.46 to 0.41; $p = 0.913$), but the VATS group had lower pain scores on day 2 (median 3 vs. 4, MD –0.54, 95% CI –0.99 to –0.09; $p = 0.018$). There was no evidence to suggest that the difference between groups differed by type of analgesia (test for interaction $p = 0.19$). Pain scores did not vary significantly with type of thoracotomy, use of muscle sparing or not, rib resection or not, or number of VATS port sites. Analgesic consumption was 10% lower in the VATS group (mean ratio 0.9, 95% CI 0.80 to 1.01).

Incision pain beyond 5 weeks

Prolonged incision pain was less common in the VATS group (relative risk 0.82, 95% CI 0.72 to 0.94; $p = 0.003$).

Time from surgery to hospital discharge

Median stay was lower in the VATS group [4 vs. 5 days, hazard ratio (HR) 1.34, 95% CI 1.09 to 1.65; $p = 0.006$]. The median time to first meeting predefined 'fit-for-discharge' criteria was 1 day earlier than the median stay in both groups. The proportion of patients discharged 'early' was similar (8.4% overall). Discharge was 'delayed' in one-quarter of participants.

Overall survival and progression-free survival to 1 year

There were 31 deaths (VATS, $n = 13$; open surgery, $n = 18$; HR 0.67, 95% CI 0.32 to 1.40; $p = 0.28$). Thirty-three participants (VATS, $n = 16$; open surgery, $n = 17$) experienced disease recurrence (HR 0.73, 95% CI 0.42 to 1.27; $p = 0.26$). There were 24 cases of locoregional recurrence (VATS, $n = 11$; open surgery, $n = 13$), 17 cases of distant recurrence (VATS, $n = 7$; open surgery, $n = 10$) and 10 cases of new cancer (VATS, $n = 4$; open surgery, $n = 6$).

Uptake of adjuvant treatment

A total of 73 participants had adjuvant treatment, 56 of whom met the eligibility criteria defined by the National Institute for Health and Care Excellence. Time to uptake of adjuvant treatment was similar in both groups (HR 1.12, 95% CI 0.62 to 2.02; $p = 0.716$ for eligible subset).

EORTC QLQ-C30 quality-of-life questionnaire

Global health status, role and social functioning were all significantly higher in the VATS group than in the open-surgery group, and where cognitive function was impaired, the impairment was less. The effect of surgery on emotional function varied over time. At 2 weeks, fewer participants in the VATS

group than in the open-surgery group reported impaired emotional function, but thereafter the results were similar. The improvement in physical functioning was more marked in the early discharge period and less pronounced after 6 months. On average, the score was 4.22 points higher in the VATS group than in the open-surgery group (95% CI 1.48 to 6.97 points; $p = 0.009$).

Participants randomised to VATS experienced less pain and fatigue and had less difficulty sleeping in the first 2 weeks than participants randomised to open surgery. These participants were also less likely to experience appetite loss and nausea, and constipation in the early period post surgery. Other measures were similar in the two groups. Pain scores to 1 year were significantly higher in participants who had rib resection than in patients who did not (MD 9.8, 95% CI 2.07 to 17.52).

EORTC QLQ-LC13 quality-of-life questionnaire

Participants randomised to VATS experienced significantly less pain in the chest and arm at 5 weeks than participants randomised to open surgery, but other outcomes (i.e. cough, dyspnoea, alopecia, peripheral neuropathy, dysphagia, sore mouth and haemoptysis) were similar in the two groups.

EQ-5D-5L utility score

EQ-5D-5L median scores were higher in the VATS group than in the open-surgery group at all time points. Participants in the VATS group were less likely to have less than perfect health (i.e. a score < 1) (odds ratio 0.57, 95% CI 0.38 to 0.86; $p = 0.007$) than participants in the open-surgery group, and of those with less than perfect health, participants in the VATS group had, on average, higher scores (better health) than participants in the open-surgery group (geometric mean ratio 0.90, 95% CI 0.84 to 0.96; $p = 0.003$).

Adverse events

Eighty-one (32.8%) participants in the VATS group and 113 (44.3%) participants in the open-surgery group experienced at least one adverse event before hospital discharge (relative risk 0.74, 95% CI 0.66 to 0.84; $p < 0.001$), but the proportions of patients experiencing serious adverse events (SAEs) were similar (8.1% vs. 8.2%). Participants in the VATS group had fewer infective (relative risk 0.89, 95% CI 0.84 to 0.94), psychiatric (relative risk 0.98, 95% CI 0.97 to 1.00) and renal (relative risk 0.96, 95% CI 0.91 to 1.00) complications than participants in the open-surgery group. There were seven deaths before hospital discharge (VATS, $n = 2$; open surgery, $n = 5$).

Seventy-five (30.7%) participants allocated to VATS and 94 (37.8%) participants allocated to open surgery experienced at least one SAE after hospital discharge (relative risk 0.81, 95% CI 0.66 to 1.00; $p = 0.053$), of which 158 (93.5%) resulted in a hospital admission. There were 24 deaths after hospital discharge (VATS, $n = 11$; open surgery, $n = 13$), half of which were due to disease progression.

Economic evaluation

The mean QALY gain up to 1 year was 0.841 in the VATS group and 0.780 in the open-surgery group (MD 0.060, 95% CI 0.029 to 0.092). The total cost of care was £10,879 in the VATS group and £13,581 in the open group (MD -£2702, 95% CI -£5632 to £228). The probability that VATS is cost-effective at a willingness-to-pay threshold of £20,000 per QALY is > 0.99 .

Discussion

Main findings

Video-assisted thoracoscopic surgery lobectomy was associated with less pain, fewer complications and a shorter hospital stay than open surgery, without any compromise to oncologic outcome. The benefits extended beyond the in-hospital period. Physical function at 5 weeks was significantly improved in the VATS group and was consistent for all secondary measures of quality of life up to 1 year. There were

fewer readmissions in the VATS group than in the open-surgery group, and no difference in survival. VATS was also cost-effective at all thresholds.

One concern about keyhole surgery has been the ability to perform a cancer operation adequately. The quality of the lymph node harvesting and similar rates of lymph node upstaging and complete pathological resection confirm the completeness of the operation. Comparable survival provides further assurance on the longer-term oncologic safety of a VATS approach.

Strengths and limitations

Strengths include the ability to successfully blind the procedure and the ability to train surgeons in the communication skills required to successfully recruit patients. Ethnic minorities were under-represented compared with the UK population, but surgical technique is not influenced by ethnicity and the cohort reflected the ethnicity of people with lung cancer.

Conclusion

For patients with early-stage lung cancer in whom a lobectomy is proposed, our results strongly support the use of VATS as the procedure of choice. The clinical benefits were achieved without any compromise to important oncologic outcomes and the procedure provides excellent value for money for the NHS. It is important that thoracic surgeons have appropriate opportunities for training in minimally invasive surgical techniques.

Areas for further research include a meta-analysis of long-term survival (\approx 1800 participants when all trials are completed) and an evaluation of the clinical efficacy of robotic VATS surgery.

Trial registration

This trial is registered as ISRCTN13472721.

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