Outcomes of single- versus multi-port video-assisted thoracoscopic surgery: Data from a multicenter randomized controlled trial of video-assisted thoracoscopic surgery versus thoracotomy for lung cancer

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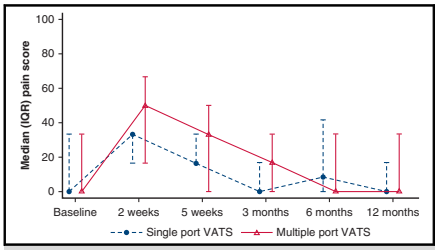
ABSTRACT

Objectives: Surgery through a single port may be less painful because access is supplied by 1 intercostal nerve or more painful because multiple instruments are used in 1 port. We analyzed data collected from the video-assisted thoracoscopic surgery group of a randomized controlled trial to compare differences in pain up to 1 year.

Methods: Groups were compared in a prespecified exploratory analysis using direct (regression) and indirect comparison (difference with respect to thoracotomy). In-hospital visual analogue scale pain scores were used, and analgesic ratios were calculated. After discharge, pain was evaluated using European Organization for Research and Treatment of Cancer Quality of Life Questionnaires-Core 30 scores up to 1 year.

Results: From July 2015 to February 2019, we randomized 503 participants. After excluding 50 participants who did not receive lobectomy, surgery was performed using a single port in 42 participants (predominately by a single surgeon), multiple ports in 166 participants, and thoracotomy in 245 participants. No differences were observed in-hospital between single- and multiple-port video-assisted thoracoscopic surgery when modeled using a direct comparison, mean difference of −0.24 (95% CI, −1.06 to 0.58) or indirect comparison, mean difference of −0.33 (−1.16 to 0.51). Mean analgesic ratio (single/multiple port) was 0.75 (0.64 to 0.87) for direct comparison and 0.90 (0.64 to 1.25) for indirect comparison. After discharge, pain for single-port video-assisted thoracoscopic surgery was lower than for multiple-port video-assisted thoracoscopic surgery (first 3 months), and corresponding physical function was higher up to 12 months.

Conclusions: There were no consistent differences for in-hospital pain when lobectomy was undertaken using 1 or multiple ports. However, better pain scores and physical function were observed for single-port surgery after discharge. (JTCVS Open 2024;19:296-308)



Raw QLQ-C30 pain scores over time.

CENTRAL MESSAGE

There were no consistent differences for in-hospital pain when lobectomy for lung cancer was undertaken using 1 or multiple ports. However, better pain scores and physical function were observed for single-port surgery after discharge.

PERSPECTIVE

Surgery through a single port supplied by 1 intercostal nerve may be less painful (and lead to a faster recovery) or more painful as multiple instruments pass through 1 access. We analyzed subgroup data from a randomized controlled trial and determined no differences for in-hospital pain, but lower pain and better physical function for single-port surgery after discharge.

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Abbreviations and Acronyms

QLQ-C30 = Quality of Life Questionnaires-Core 30
VATS = video-assisted thoracoscopic surgery
VIOLET = VIdeo assisted thoracoscopic lobectomy versus conventional Open LobEcTomy for lung cancer

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The VIdeo assisted thoracoscopic lobectomy versus conventional Open LobEcTomy for lung cancer (VIOLET) is a multicenter randomized controlled trial carried out in the United Kingdom comparing video-assisted thoracoscopic surgery (VATS) with open (thoracotomy) surgery for lung cancer that reported VATS lobectomy was associated with less pain and better recovery of physical function (as a global marker of recuperation) in the 5 weeks after randomization compared with open surgery.[1]

A central hypothesis for VIOLET was that operating through small incisions without rib spreading may be less painful, leading to faster recovery compared with open surgery that involves rib spreading and traction to thoracic nerves. On the same premise, it is postulated that surgery through a single port supplied by 1 intercostal nerve may be less painful (and lead to a faster recovery) compared with the use of multiple ports affecting many intercostal nerves (alternatively, single-port VATS may be more painful because multiple instruments are placed into 1 incision).

To investigate this hypothesis, we analyzed data collected from VIOLET to complete prespecified exploratory analyses comparing the pain of lobectomy for lung cancer using 1 versus multiple ports.

MATERIAL AND METHODS

Details of the VIOLET protocol have been published,[2] and a copy of the statistical analysis plan is available accompanying the full text article at *New England Journal of Medicine Evidence*.[1] The trial was approved by the Research Ethics Committee London–Dulwich (reference 14/LO/2129) on January 7, 2015. All participants gave written informed consent before joining the trial. No individual patient data were published in this study; the consent to publication and dissemination of data is based on trial participation consent as per UK research ethics committee approval.

In brief, we enrolled patients with confirmed or suspected primary lung cancer within clinical stage cT1-3, cN0-1, cM0. Participants were randomized in a 1:1 ratio to VATS or open surgery using a secure internet-based system (Sealed Envelope Ltd), stratified by center and minimized by surgeon. VATS was defined as a procedure undertaken using a telescope for visualization and instruments introduced in 1 to 4 port incisions without rib spreading, and open surgery was defined as a procedure undertaken through direct vision using a single thoracotomy incision with rib spreading (rib resection was permitted but not mandated).

After surgery, participants and assessors were blinded using a wound dressing sufficiently large to conceal a thoracotomy incision (regardless of actual surgical access used). Centers declared analgesia practices and were asked to standardize the analgesic protocol for all participants. All other aspects of postoperative care were conducted in accordance with the center's usual practice.

A prespecified exploratory analysis was stated in our original protocol to compare pain scores within the VATS lobectomy group by single- versus multiple-port sites analyzed by treatment received.[2] In hospital, visual analogue scale pain scores were used to assess pain, but are not an independent measure of pain; therefore, we also screened analgesic ratios for any differential analgesic use that could impact the reporting of pain. After discharge, pain and physical functioning were evaluated using participants self-reporting of European Organization for Research and Treatment of Cancer Quality of Life Questionnaires-Core 30 (QLQ-C30) captured at 2 weeks, 5 weeks, 3 months, 6 months, and 12 months.

Comparisons of pain, analgesic use, and physical functioning between the single- versus multiple-port groups were undertaken (a) directly using a 3-level categorical variable (1 port, multiple ports, and thoracotomy), adjusting for center and surgeon where possible but discarding any effect of randomization, and (b) indirectly by comparing estimates of (i) single-port versus thoracotomy and (ii) multiple-port versus thoracotomy to preserve the effects of randomization that includes within-center and within-surgeon practice.

Pain scores and physical functioning were analyzed using linear mixed-effects models. Analgesic use was compared by calculating mean ratios for each analgesic group and estimating 95% CIs using bootstrapping. For indirect analyses, a port technique was assigned for each surgeon based on the most frequently performed technique to ensure each surgeon was included in only 1 of the analyses (I or ii above) to be included in the indirect comparison (Table 1). Further details are provided in the Appendix E1. Sensitivity analyses were performed by adding baseline characteristics with standardized mean differences for single versus multiple ports greater than 0.5 to the models. Statistical analyses were performed using Stata, version 16.1 (StataCorp LLC).

This study is funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment program (Reference Number 13/04/03). This trial was designed and delivered in collaboration with the Bristol Trials Centre, a UK Clinical Research Collaboration–registered clinical trials unit, which is in receipt of NIHR clinical trials unit support funding, and the Bristol Royal College of Surgeons Trials Centre. The research team acknowledges the support of the NIHR Clinical Research Network and the UK Thoracic Surgery Research Collaborative. The views and opinions expressed are those of the authors and do not necessarily reflect those of the NIHR Health Technology Assessment program, the NHS, or the Department of Health and Social Care.

This trial is registered as ISRCTN13472721.

The trial was approved by the Research Ethics Committee London–Dulwich (reference 14/LO/2129) on January 7, 2015.

All study participants gave written informed consent before joining the trial.

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TABLE 1. Surgeon port technique for indirect analyses

Surgeon	Single port (n = 42)	Multiple ports (n = 166)	Thoracotomy (n = 245)	Surgeon port technique
Surgeon 1	30	6	44	Single port
Surgeon 2	2	28	29	Multiple port
Surgeon 3	0	26	30	Multiple port
Surgeon 4	0	15	18	Multiple port
Surgeon 5	0	15	17	Multiple port
Surgeon 6	0	14	12	Multiple port
Surgeon 7	0	12	14	Multiple port
Surgeon 8	0	9	11	Multiple port
Surgeon 9	0	9	10	Multiple port
Surgeon 10	0	7	8	Multiple port
Surgeon 11	0	6	6	Multiple port
Surgeon 12	4	0	8	Single port
Surgeon 13	0	3	7	Multiple port
Surgeon 14	0	4	5	Multiple port
Surgeon 15	0	3	4	Multiple port
Surgeon 16	3	0	4	Single port
Surgeon 17	0	3	3	Multiple port
Surgeon 18	0	1	4	Multiple port
Surgeon 19	2	0	2	Single port
Surgeon 20	1	0	3	Single port
Surgeon 21	0	1	2	Multiple port
Surgeon 22	0	2	0	-
Surgeon 23	0	1	1	Multiple port
Surgeon 24	0	1	1	Multiple port
Surgeon 25	0	0	2	-

Surgeons 22 and 25 were not included in the indirect analyses because they did not perform both VATS and thoracotomy procedures.

RESULTS

From July 2015 to February 2019, we randomized 503 participants. After excluding 50 participants who did not receive a lobectomy, surgery was performed using single-port access in 42 participants, multiple-port access in 166 participants, and thoracotomy in 245 participants. The baseline characteristics and surgical details are presented in Table 2.

In-Hospital Outcomes

On day 1, the median pain score was 3 for single-port VATS, 4 for multiple-port VATS, and 4 for a thoracotomy, and by day 2 it was 3 for both VATS groups versus 4 for the thoracotomy group (Table 3). No differences were observed between single- and multiple-port VATS when modeled using a direct comparison, with a mean difference of −0.24 (95% CI, −1.06 to 0.58) or indirect comparison with a mean difference of −0.33 (95% CI, −1.16 to 0.51; Table 4). Sensitivity analyses, adding baseline Eastern Cooperative Oncology Group status (standardized mean difference of 0.55) and cT stage (primary tumor stage, standardized mean difference of 0.65) to the models, provided results that were consistent with the primary analyses (Table E1). The mean analgesic ratio (single/multiple port) was 0.75 (95% CI, 0.64-0.87) for direct comparison and 0.90 (95% CI, 0.64-1.25) for indirect comparison (Table 4).

There was no difference in the median (interquartile range) length of stay for participants receiving single- and multiple-port VATS, which was 4 days (3-8) and 4 days (3-7), respectively, compared with 5 days (4-8) for thoracotomy (Table E2).

Long-Term Outcomes

After discharge, median pain scores for the single-port VATS were observed to be lower than for multi-port VATS up to 6 months postrandomization (Figure 1, Table E3). The greatest difference was observed at 2 weeks when modeled by direct comparison (mean difference of −11.8 [95% CI, −22.0 to −1.5]); although this difference

TABLE 2. Baseline characteristics and surgical details

Baseline characteristic	Single-port VATS (n = 42)	Multi-port VATS (n = 166)	Thoracotomy (n = 245)	SMD single-port vs multi-port VATS
Age, y	68 (9.7)	69 (8.2)	70 (8.2)	−0.20
Male	24/42 (57.1%)	72/166 (43.4%)	129/245 (52.7%)	0.28
Clinical stage				
cT				0.65
1a	7/42 (16.7%)	11/166 (6.6%)	14/245 (5.7%)	
1b	15/42 (35.7%)	47/166 (28.3%)	76/245 (31.0%)	
1c	12/42 (28.6%)	42/166 (25.3%)	70/245 (28.6%)	
2a	7/42 (16.7%)	36/166 (21.7%)	50/245 (20.4%)	
2b	1/42 (2.4%)	12/166 (7.2%)	16/245 (6.5%)	
3	0/42 (0.0%)	18/166 (10.8%)	19/245 (7.8%)	
cN				0.02
0	39/42 (92.9%)	155/166 (93.4%)	229/245 (93.5%)	
1	3/42 (7.1%)	11/166 (6.6%)	16/245 (6.5%)	
ECOG status				0.55
0	33/42 (78.6%)	91/164 (55.5%)	161/242 (66.5%)	
1	7/42 (16.7%)	65/164 (39.6%)	74/242 (30.6%)	
2	2/42 (4.8%)	7/164 (4.3%)	6/242 (2.5%)	
3	0/42 (0.0%)	1/164 (0.6%)	1/242 (0.4%)	
Mean predicted lung function, %				
FEV1*	83 (19.5)	82 (19.0)	82 (21.4)	0.06
FVC†	97 (17.5)	94 (17.0)	95 (18.6)	0.15
TLco‡	74 (17.8)	74 (29.3)	72 (20.5)	0.01
Surgical details				
Operative time (h)§	2.7 (2.1-3.1)	2.5 (2.0-3.1)	2.3 (1.8-2.8)	0.04
No. of VATS ports				
1 port	42/42 (100.0%)	0/166 (0.0%)	-	
2 ports	0/42 (0.0%)	18/166 (10.8%)	-	
3 ports	0/42 (0.0%)	120/166 (72.3%)	-	
4 ports	0/42 (0.0%)	28/166 (16.9%)	-	
Type of thoracotomy performed				
Posterolateral thoracotomy	-	-	173/245 (70.6%)	
Anterior thoracotomy	-	-	72/245 (29.4%)	

Data are presented as median (interquartile range), mean (SD), or n/N (%). Missing data (single, multiple, thoracotomy): *11 patients with missing data (2, 4, 5). †13 patients with missing data (3, 4, 6). ‡105 patients with missing data (6, 47, 52). §1 patient with missing data (0, 0, 1). *VATS*, Video-assisted thoracoscopic surgery; *SMD*, standardized mean difference; *ECOG*, Eastern Cooperative Oncology Group; *FEV1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *TLco*, transfer capacity of the lung.

was comparable, it was not statistically significant when modeled by indirect comparison (mean difference of −10.5 [95% CI, −23.1 to 2.1]; Table E4). Results were unaltered after sensitivity analyses (Table E5).

Correspondingly, median physical functioning scores were higher for single-port VATS compared with multiple-port VATS (Figure 2). Modeling by direct comparison gave a mean difference of 5.75 (95% CI, 0.69-10.82); again,

TABLE 3. VAS pain scores in first 2 days postsurgery

Outcome	Time	Single-port VATS (n = 42)	Multi-port VATS (n = 166)	Thoracotomy (n = 245)
VAS pain score	Baseline*	0 (0.0-1.0)	0 (0.0-2.0)	0 (0.0-1.0)
	Day 1†	3 (2.0-5.0)	4 (2.0-6.0)	4 (2.0-6.0)
	Day 2‡	3 (1.0-5.0)	3 (0.0-5.0)	4 (2.0-5.0)

Data are presented as median (IQR). Missing data (single-port VATS, multi-port VATS, thoracotomy): *17 patients with missing data (1, 7, 9). †17 patients with missing data (3, 7, 7). ‡33 patients with missing data (6, 13, 14). *VAS*, Visual analogue scale; *VATS*, video-assisted thoracoscopic surgery.

TABLE 4. Direct and indirect comparisons of in-hospital pain and analgesic use

Comparator	Direct comparison	Indirect comparison*
VAS pain scores in first 2 days†		
Single-port VATS vs thoracotomy	−0.60 (−1.36 to 0.17)	−0.65 (−1.34 to 0.04)
Multi-port VATS vs thoracotomy	−0.36 (−0.78 to 0.06)	−0.33 (−0.79 to 0.14)
Single-port VATS vs multi-port VATS	−0.24 (−1.06 to 0.58)	−0.33 (−1.16 to 0.51)
Analgesic mean ratio for the hospital stay‡		
Single-port VATS vs thoracotomy	0.72 (0.61-0.84)	0.80 (0.58-1.10)
Multi-port VATS vs thoracotomy	1.01 (0.87-1.16)	0.89 (0.77-1.02)
Single-port VATS vs multi-port VATS	0.75 (0.64-0.87)	0.90 (0.64-1.25)

Data are mean difference (95% CI) or mean ratio (95% CI). *VAS*, Visual analogue scale; *VATS*, video-assisted thoracoscopic surgery. *For indirect comparison, single-port VATS versus multi-port VATS was estimated using the branches (1) single-port VATS versus thoracotomy and (2) multi-port VATS versus thoracotomy. †MD, global *P* value for all 3 groups from direct comparison, $P = .11$. Multiple imputation (100 imputed datasets) was used to account for missing data. ‡Mean ratio, the average total analgesic dosage in VATS divided by thoracotomy groups.

this difference was comparable but not statistically significant when modeled by indirect comparison (mean difference, 3.68 [95% CI, −2.51 to 9.88]; Tables E6 and E7). Sensitivity analyses showed similar results (Table E8).

DISCUSSION

The results of our work suggest no difference in early (in-hospital) pain scores comparing single- versus multiple-port surgery undertaken for lobectomy for primary lung cancer. Pain scores were observed to be lower for single-port access in the first 3 months of follow-up, before becoming comparable from that point up to 1 year, whereas physical function was observed to be better up to 1 year.

Pain is a complex outcome to analyze because it is dependent on raw visual analogue scores and the amount of analgesia required to achieve it; for example, 1 access can be considered "less painful" than the other even with the same pain score if less analgesics were used. We observed a 1-point difference in pain score in favor of single-port surgery on the first postoperative day and used 2 methods to compare the amount of analgesia used. We also surveyed our patients at discharge (when bandages were removed), and the correct "guess" rate was no better than chance at approximately 50% between open and keyhole surgery. As such, we are relatively confident that patients would be unlikely to appreciate if they had 1 or multiple ports.

Although the results were consistent in the direction of effect (in favor of single port), they were inconsistent in the magnitude of effect and the variance (certainty) of the estimate. The analgesic ratio was 25% less and statistically significant on direct comparison (that does not take account of randomization) and 10% less without statistical significance on indirect comparison (that takes randomization into account). In this setting, we would argue that the indirect comparison is likely to be more representative. Direct comparisons of analgesic ratios are undertaken as if the operations were all performed as independent procedures, but the success of pain management can vary between surgeons, for example, better pain control by surgeons using single-port (vs surgeons using multi-port) with intercostal and paravertebral analgesic blockade. Indirect comparison compares analgesic ratios using thoracotomy as control such that the same surgeon performing single-port versus thoracotomy is compared with other surgeons performing multi-port versus thoracotomy to reduce between surgeon/procedure biases (it is assumed that the same surgeon would have an equal mindset and the skills to manage analgesia for patients undergoing VATS and open surgery under their care). The indirect comparison results are known to agree better with direct comparison randomized trials,[3] and we found this to be the case when compared with the study by Perna and colleagues,[4] a randomized head-to-head comparison of single- versus multiple-port surgery reporting no differences in pain score or morphine use, as well as the conclusion of a meta-analysis of (mainly) nonrandomized and randomized studies.[5]

It is interesting to note the differences in pain within the first 3 months of surgery, although not statistically significant, were in favor of single-port surgery. The lower pain scores were associated with higher physical function implying consistency in the observed effect. A 5% (or 5-point) difference in the European Organization for Research and Treatment of Cancer QLQ-C30 scale, which we broadly estimate (based on the published figure by Bade and colleagues[6]) to correspond to 1250 daily steps. We

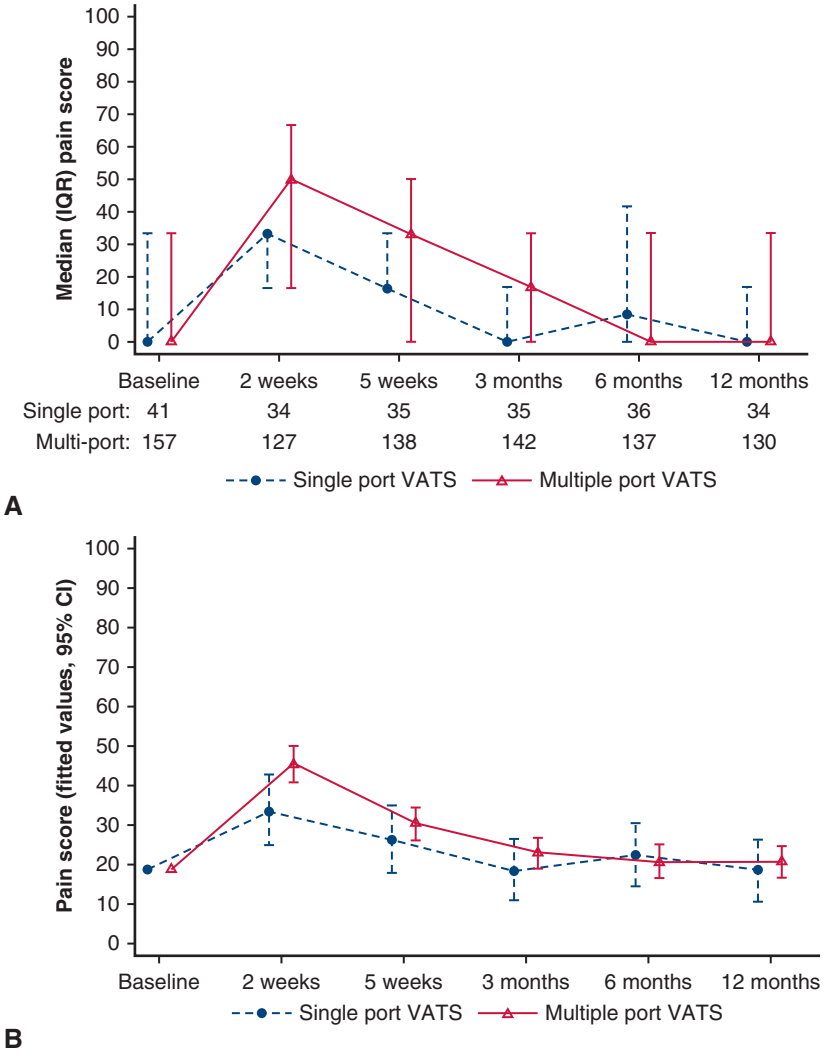

FIGURE 1. A, Raw QLQ-C30 pain scores over time. B, Fitted values of QLQ-C30 pain score derived from linear mixed effect model. Pain score fitted values are derived from the direct comparison linear mixed effect model including a time by treatment interaction. Test for time by treatment interaction, $P = .054$. *VATS*, Video-assisted thoracoscopic surgery.

hypothesize that better outcomes may be due to the favorable effects of the (less painful) single-port surgery, and the differences in pain scores of 10 points (which can be interpreted as the difference of 1 point on a visual analogue scale) within the first 2 weeks and improved physical function are due to patients having to manage their own pain at home (compared with self or supervised analgesic management in-hospital).

After the 3-month time point, pain was comparable up to 1 year, and this may be indicative of the duration of wound healing, whereas physical function appeared to be more consistently improved.

Study Limitations

The obvious limitation to our work is that it is a nonrandomized comparison of results from a randomized trial (and does not carry the same weight of evidence), but we attempted to mitigate bias (in part) through indirect comparisons. This is important because the majority of the single-port operations were performed by 1 surgeon and therefore comparing the within surgeon differences (gradient of difference for the same surgeon between VATS and thoracotomy) is important rather than between surgeons (gradient of difference between surgeons who perform single- and multi-port VATS). There were 2 surgeons who performed single- and multi-port procedures, and for direct comparisons, all outcomes were assigned to the number of ports (single vs multiple) as opposed to surgeon alone. For indirect comparisons, a port technique was assigned to each surgeon to ensure they were included in only 1 of the single- or multi-port versus thoracotomy analyses.

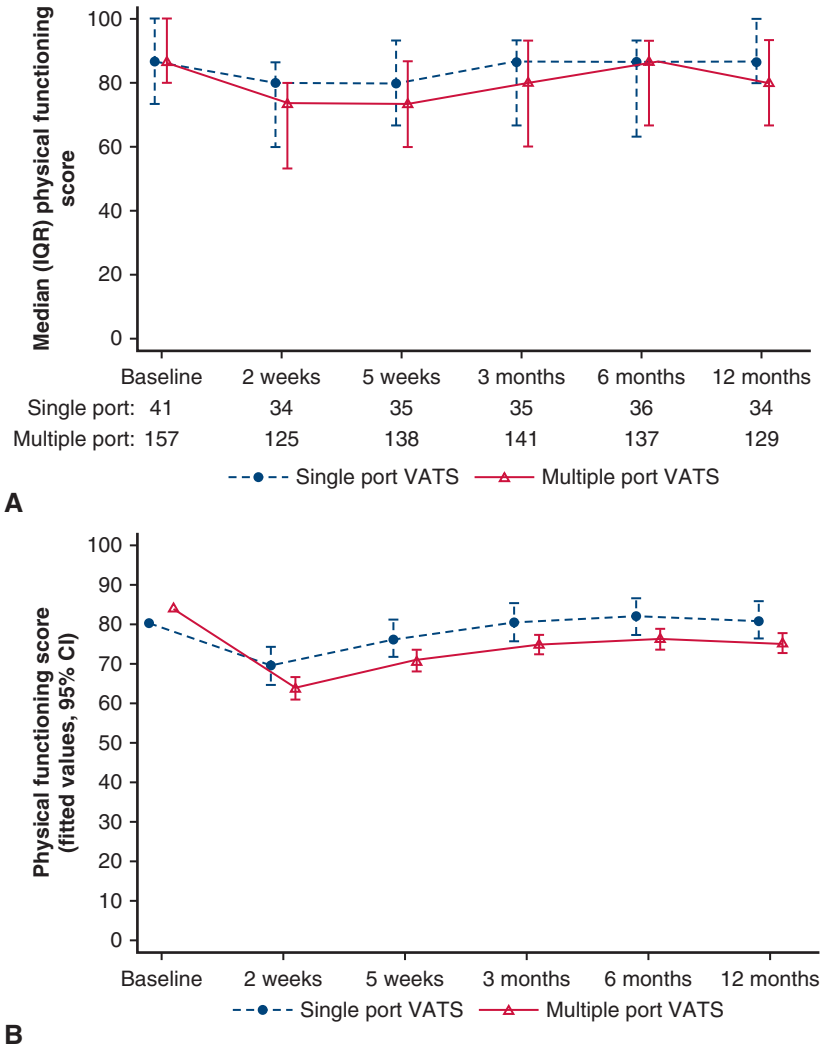

FIGURE 2. A, Raw QLQ-C30 physical functioning score over time. B, Fitted values of QLQ-C30 physical functioning scores derived from linear mixed effects model. Physical functioning score fitted values are derived from the direct comparison linear mixed effect model. Test for time by treatment interaction, $P = .42$. *VATS*, Video-assisted thoracoscopic surgery.

Pain associated with single- versus multi-port surgery was a prespecified exploratory analysis within the VIOLET trial,[2] but was not powered to detect differences in pain or analgesic use; as such, we are not certain as to the minimum important difference (if any) for the 2 comparisons. In addition, we did not stipulate the exact operation technique for 1 or more ports, neither did we measure or account for recreational drug or alcohol use, or different lengths of incision size that may influence pain outcomes.

Many surgeons question if single- versus multi-port comparisons remains an important question,[7] and we would argue that it does, because a reduction in pain may be an important contributor to the observed reduction in complications (compared with thoracotomy) in VIOLET.[1] Other randomized trials are under way to continue to add to the evidence and clarify the answer.[8]

CONCLUSIONS

There were no consistent observable differences for in-hospital pain when lobectomy for lung cancer was undertaken using 1 or multiple ports. However, better pain scores and function were observed for single-port surgery after discharge for pain (up to 3 months) and physical function (up to 12 months).

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://www.aats.org/resources/outcomes-of-

single-versus-multi-port-vats-data-from-violet-a-uk-multi-centre-rct-of-vats-versus-thoracotomy-for-lung-cancer-surgery.

Conflict of Interest Statement

E.L. reports personal fees from Abbott Molecular, GlaxoSmithKline plc, Pfizer Inc, Novartis Pharmaceuticals UK Ltd, Medtronic plc/Covidien, Roche Diagnostics, Lilly Oncology, Boehringer Ingelheim, Medela, Johnson & Johnson/Ethicon, AstraZeneca, and Bristol-Myers Squibb; grants from Clearbridge BioMedics, Illumina, and Guardant Health; and grants and personal fees from ScreenCell outside the submitted work. In addition, E.L. has patents P52435GB and P57988GB issued to Imperial Innovations. T.B. reports personal fees from Johnson & Johnson, Medtronic plc, Medela, and AstraZeneca outside the submitted work. J.D. reports personal fees from Cambridge Medical Robotics, ArtiSential, and Medtronic plc/Covidien outside the submitted work. All other authors reported no conflicts of interest.

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Key Words: multi-port VATS, postoperative pain, single-port VATS

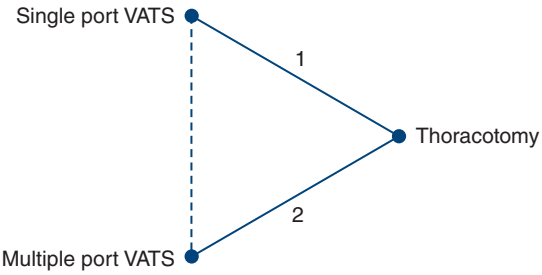
APPENDIX E1: STATISTICAL METHODS – ADDITIONAL INFORMATION

Linear Mixed Effects Models

Linear mixed effects models were used to analyze VAS pain scores in the first 2 days postsurgery: QLQ-C30 pain scores and QLQ-C30 physical functioning scores. A time by treatment interaction was added to all models. Overall treatment effects are provided unless the interaction reached 10% statistical significance, in which case treatment effects for each time point are presented as was the case for reporting postdischarge pain.

Indirect Analyses

Indirect analyses of single-port VATS versus multi-port VATS were performed using branches (1) single-port VATS versus thoracotomy and (2) multi-port VATS versus thoracotomy (see Figure below). Treatment estimates from branches 1 and 2 were pooled using a fixed effects model.



The dashed line represents an indirect comparison.

TABLE E1. Sensitivity analyses: Direct and indirect comparisons of VAS pain score in first 2 days postsurgery

Comparison	Direct comparison MD (95% CI)	Indirect comparison* MD (95% CI)
Single-port VATS vs thoracotomy	−0.71 (−1.47 to 0.05)	−0.73 (−1.43 to −0.02)
Multi-port VATS vs thoracotomy	−0.39 (−0.81 to 0.03)	−0.36 (−0.83 to 0.10)
Single-port VATS vs multi-port VATS	−0.32 (−1.13 to 0.49)	−0.36 (−1.21 to 0.48)

Multiple imputation (100 imputed datasets) was used to account for missing data. *VAS*, Visual analogue scale; *MD*, mean difference; *VATS*, video-assisted thoracoscopic surgery. *For indirect comparison, single-port VATS versus multi-port VATS was estimated using the branches (1) single-port VATS versus thoracotomy and (2) multi-port VATS versus thoracotomy. Sensitivity analyses adjust for Eastern Cooperative Oncology Group status and cT stage (primary tumor).

TABLE E2. Clinical outcomes

Outcome	Single-port VATS (n = 42)	Multi-port VATS (n = 166)	Thoracotomy (n = 245)
Efficacy outcomes			
Length of hospital stay (d)	4 (3-8)	4 (3-7)	5 (4-8)
Discharged with a drain	4/42 (9.5%)	18/166 (10.8%)	27/245 (11.0%)
Drain duration (d)*	2 (1-5)	2 (1-4)	2 (2-4)
Oncologic outcomes			
Total no. of lymph node stations harvested	5 (4.0-6.0)	5 (4.0-6.0)	5 (4.0-6.0)
Mediastinal nodes harvested (stations 2-9)	4 (3.0-4.0)	3 (3.0-4.0)	3 (3.0-4.0)
Safety outcomes			
Any in-hospital adverse event	15/42 (35.7%)	52/166 (31.3%)	117/245 (47.8%)
Any in-hospital SAE	1/42 (2.4%)	10/166 (6.0%)	29/245 (11.8%)
Postdischarge SAEs (events/patients)	21/13 (31.0%)	112/56 (34.1%)	209/95 (39.7%)
Any readmission (events/patients)	19/13 (31.0%)	90/52 (32.3%)	143/88 (37.4%)

Data are presented as median (IQR), n/N (%), or events/patients (%). *VATS*, Video-assisted thoracoscopic surgery; *SAE*, Serious adverse event. *Only available for patients with all drains removed before discharge.

TABLE E3. Quality of Life Questionnaires-Core 30 pain scores over time

Outcome	Time	Single-port VATS (n = 42)	Multi-port VATS (n = 166)	Thoracotomy (n = 245)
QLQ-C30 pain scores	Baseline*	0 (0.0-33.3)	0 (0.0-33.3)	0 (0.0-33.3)
	2 wk†	33 (16.7-33.3)	50 (16.7-66.7)	67 (33.3-83.3)
	5 wk‡	17 (16.7-33.3)	33 (0.0-50.0)	33 (16.7-66.7)
	3 mo§	0 (0.0-16.7)	17 (0.0-33.3)	25 (0.0-50.0)
	6 mo‖	8 (0.0-41.7)	0 (0.0-33.3)	17 (0.0-33.3)
	12 mo¶	0 (0.0-16.7)	0 (0.0-33.3)	17 (0.0-50.0)

Data are presented as median (IQR). Missing data (single-port VATS, multi-port VATS, thoracotomy): *21 patients with missing data (1, 9, 11). †103 patients with missing data (8, 39, 56). ‡58 patients with missing data (7, 28, 23). §70 patients with missing data (7, 24, 39). ‖78 patients with missing data (6, 29, 43). ¶103 patients with missing data (8, 36, 59). *VATS*, Video-assisted thoracoscopic surgery; *QLQ-C30*, Quality of Life Questionnaires-Core 30.

TABLE E4. Direct and indirect comparisons of Quality of Life Questionnaires-Core 30 pain scores

Comparison	Time point	Direct comparison MD (95% CI)	Indirect comparison* MD (95% CI)
Single-port VATS vs thoracotomy	2 wk	−24.9 (−34.7 to −15.1)	−23.0 (−33.6 to −12.4)
Multi-port VATS vs thoracotomy	2 wk	−13.2 (−19.2 to −7.1)	−12.5 (−19.4 to −5.7)
Single-port VATS vs multi-port VATS	2 wk	−11.8 (−22.0 to −1.5)	−10.5 (−23.1 to 2.1)
Single-port VATS vs thoracotomy	5 wk	−15.5 (−24.5 to −6.6)	−15.4 (−26.1 to −4.6)
Multi-port VATS vs thoracotomy	5 wk	−11.4 (−16.7 to −6.1)	−11.4 (−17.2 to −5.6)
Single-port VATS vs multi-port VATS	5 wk	−4.1 (−13.4 to 5.2)	−4.0 (−16.2 to 8.3)
Single-port VATS vs thoracotomy	3 mo	−10.7 (−19.0 to −2.4)	−12.4 (−22.9 to −1.9)
Multi-port VATS vs thoracotomy	3 mo	−6.4 (−11.5 to −1.4)	−5.9 (−11.1 to −0.7)
Single-port VATS vs multi-port VATS	3 mo	−4.3 (−12.9 to 4.3)	−6.5 (−18.2 to 5.2)
Single-port VATS vs thoracotomy	6 mo	−5.2 (−14.0 to 3.6)	−8.9 (−19.5 to 1.6)
Multi-port VATS vs thoracotomy	6 mo	−7.0 (−12.4 to −1.6)	−5.7 (−11.3 to −0.03)
Single-port VATS vs multi-port VATS	6 mo	1.8 (−7.2 to 10.8)	−3.3 (−15.2 to 8.7)
Single-port VATS vs thoracotomy	12 mo	−8.2 (−16.8 to 0.5)	−10.3 (−21.1 to 0.6)
Multi-port VATS vs thoracotomy	12 mo	−6.0 (−11.3 to −0.7)	−5.4 (−11.2 to 0.3)
Single-port VATS vs multi-port VATS	12 mo	−2.2 (−11.1 to 6.7)	−4.8 (−17.2 to 7.5)

Results estimated from linear mixed effects models. Test for treatment by time interaction from direct comparison, $P = .054$; therefore, treatment effects are presented separately for each time point. Multiple imputation (50 imputed datasets) was used to account for missing data. *MD*, Mean difference; *VATS*, video-assisted thoracoscopic surgery. *For indirect comparison, single-port VATS versus multi-port VATS was estimated using the branches (1) single-port VATS versus thoracotomy and (2) multi-port VATS versus thoracotomy.

TABLE E5. Sensitivity analyses: Direct and indirect comparisons of Quality of Life Questionnaires-Core 30 pain scores

Comparison	Time point	Direct comparison MD (95% CI)	Indirect comparison* MD (95% CI)
Single-port VATS vs thoracotomy	2 wk	−26.2 (−35.9 to −16.5)	−23.8 (−34.4 to −13.3)
Multi-port VATS vs thoracotomy	2 wk	−13.3 (−19.4 to −7.3)	−12.9 (−19.8 to −6.0)
Single-port VATS vs multi-port VATS	2 wk	−12.8 (−23.1 to −2.6)	−10.9 (−23.5 to 1.6)
Single-port VATS vs thoracotomy	5 wk	−16.8 (−25.8 to −7.9)	−16.1 (−26.7 to −5.4)
Multi-port VATS vs thoracotomy	5 wk	−11.6 (−16.9 to −6.3)	−11.7 (−17.5 to −6.0)
Single-port VATS vs multi-port VATS	5 wk	−5.2 (−14.5 to 4.1)	−4.3 (−16.5 to 7.8)
Single-port VATS vs thoracotomy	3 mo	−12.1 (−20.4 to −3.8)	−13.0 (−23.5 to −2.5)
Multi-port VATS vs thoracotomy	3 mo	−6.6 (−11.6 to −1.6)	−6.2 (−11.4 to −1.1)
Single-port VATS vs multi-port VATS	3 mo	−5.5 (−14.1 to 3.2)	−6.7 (−18.4 to 4.9)
Single-port VATS vs thoracotomy	6 mo	−6.6 (−15.3 to 2.2)	−9.6 (−20.1 to 0.9)
Multi-port VATS vs thoracotomy	6 mo	−7.2 (−12.6 to −1.8)	−6.0 (−11.6 to −0.4)
Single-port VATS vs multi-port VATS	6 mo	0.6 (−8.4 to 9.6)	−3.6 (−15.5 to 8.2)
Single-port VATS vs thoracotomy	12 mo	−9.6 (−18.3 to −0.8)	−11.1 (−21.9 to −0.2)
Multi-port VATS vs thoracotomy	12 mo	−6.2 (−11.5 to −0.9)	−5.7 (−11.5 to 0.01)
Single-port VATS vs multi-port VATS	12 mo	−3.4 (−12.4 to 5.6)	−5.3 (−17.6 to 7.0)

Multiple imputation (50 imputed datasets) was used to account for missing data. *MD*, Mean difference; *VATS*, video-assisted thoracoscopic surgery. *For indirect comparison, single-port VATS versus multi-port VATS was estimated using the branches (1) single-port VATS versus thoracotomy and (2) multi-port VATS versus thoracotomy. Sensitivity analyses adjust for Eastern Cooperative Oncology Group status and cT stage (primary tumor).

TABLE E6. Quality of Life Questionnaires-Core 30 physical functioning scores over time

Outcome	Time	Single-port VATS (n = 42)	Multi-port VATS (n = 166)	Thoracotomy (n = 245)
QLQ-C30 physical functioning	Baseline*	87 (73.3-100.0)	87 (80.0-100.0)	87 (73.3-100.0)
	2 wk†	80 (60.0-86.7)	73 (53.3-80.0)	60 (40.0-73.3)
	5 wk‡	80 (66.7-93.3)	73 (60.0-86.7)	67 (53.3-80.0)
	3 mo§	87 (66.7-93.3)	80 (60.0-93.3)	73 (53.3-86.7)
	6 mo‖	87 (63.3-93.3)	87 (66.7-93.3)	80 (53.3-86.7)
	12 mo¶	87 (80.0-100.0)	80 (66.7-93.3)	74 (60.0-86.7)

Data are presented as median (IQR). Missing data (single-port VATS, multi-port VATS, thoracotomy): *21 patients with missing data (1, 9, 11). †105 patients with missing data (8, 41, 56). ‡58 patients with missing data (7, 28, 23). §72 patients with missing data (7, 25, 40). ‖78 patients with missing data (6, 29, 43). ¶104 patients with missing data (8, 37, 59). *QLQ-C30*, Quality of Life Questionnaires-Core 30; *VATS*, video-assisted thoracoscopic surgery.

TABLE E7. Direct and indirect comparisons of Quality of Life Questionnaires-Core 30 physical functioning

Comparison	Direct comparison MD (95% CI)	Indirect comparison* MD (95% CI)
Single-port VATS vs thoracotomy	10.96 (6.04-15.89)	9.40 (4.16-14.65)
Multi-port VATS vs thoracotomy	5.21 (2.21-8.21)	5.72 (2.43-9.02)
Single-port VATS vs multi-port VATS	5.75 (0.69-10.82)	3.68 (−2.51 to 9.88)

Test for treatment by time interaction from direct comparison, $P = .42$; therefore, overall treatment effects are presented. Multiple imputation (50 imputed datasets) was used to account for missing data. *MD*, Mean difference; *VATS*, video-assisted thoracoscopic surgery. *For indirect comparison, single-port VATS versus multi-port VATS was estimated using the branches (1) single-port VATS versus thoracotomy and (2) multi-port VATS versus thoracotomy.

TABLE E8. Sensitivity analyses: Direct and indirect comparison of Quality of Life Questionnaires-Core 30 physical functioning

Comparison	Direct comparison MD (95% CI)	Indirect comparison* MD (95% CI)
Single-port VATS vs thoracotomy	10.44 (5.55-15.32)	9.54 (4.29-14.79)
Multi-port VATS vs thoracotomy	6.03 (3.08-8.98)	6.13 (2.94-9.32)
Single-port VATS vs multi-port VATS	4.41 (−0.65 to 9.46)	3.41 (−2.73 to 9.55)

Multiple imputation (50 imputed datasets) was used to account for missing data. *MD*, Mean difference; *VATS*, video-assisted thoracoscopic surgery. *For indirect comparison, single-port VATS versus multi-port VATS was estimated using the branches (1) single-port VATS versus thoracotomy and (2) multi-port VATS versus thoracotomy. Sensitivity analyses adjust for Eastern Cooperative Oncology Group status and cT stage (primary tumor).