



Oncological clearance of uniportal vats for early stage non-small cell lung cancer

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Abstract: The uniportal video-assisted thoracic surgery (uVATS) approach may induce one of the least access traumas of all surgical approaches for anatomical lung resection and mediastinal lymph node staging for lung cancer. Numerous studies have shown uniportal VATS to be associated with reduce postoperative pain and analgesic requirement when compared with multiport VATS approaches. However, many in the thoracic surgical community remains skeptical of its oncological clearance, because a singular plane of visualisation and instrumentation is felt to be a hindrance to thorough mediastinal lymph node sampling or dissection. In this article, the evolutionary basis of VATS from multiportal to uniportal is explored. The existing evidence regarding oncological clearance by the uniportal approach is appraised, and the effect of surgeon experience in uniportal VATS on oncological clearance is examined. Early evidence thus far suggests that in experienced hands, the completeness of uniportal mediastinal lymph node staging is equivalent to multiportal approaches. More high-quality evidence in this arena is warranted.

Keywords: Non-small cell lung cancer (NSCLC); oncological clearance; survival; uniportal; video-assisted thoracic surgery

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Introduction

The advent of uniportal video-assisted thoracic surgery (uVATS) lobectomy in 2010 polarised the surgical community. Although it promises the least access trauma of any minimally invasive thoracic surgical approach to date, critics argue that oncological clearance may be compromised by inadequate exposure and suboptimal nodal staging. The same doubts once cast on multiportal VATS (mVATS) for resectable non-small cell lung cancer (NSCLC) in decades past have been revisited with uVATS. In this article, the state of evidence regarding oncological clearance of uVATS is examined and directions for the future are explored.

Uniportal VATS—access trauma and oncological outcomes

VATS is the term encompassing thoracic operations performed via small incisions with purely endoscopic visualisation of intrathoracic viscera. In contrast, open lobectomy is performed under direct vision through a large thoracotomy. The muscle splitting, rib cutting and spreading required to gain access to the pleural cavity by the open approach often result in chronic pain, shoulder dysfunction and disability (1). The access trauma incurred and the resultant systemic inflammatory response syndrome (SIRS) is usually severe. VATS not only reduces pain and disability, but also could limit the magnitude of SIRS. This

is hypothesised to reduce postoperative disturbances in cellular and humoral immunity and prevent an environment which could favour tumour micrometastases (2-4). Thus, reducing the incision length may potentially not only reduce pain, but also reduce immune dysfunction and possibly risks of disease recurrence. To evolve from multiportal to uniportal VATS could be an approach to benefit from such access trauma reduction. There is early data to suggest that uniportal VATS may be associated with an attenuated post-operative immunochemokine response compared with multiportal, however more studies are needed to confirm this and to investigate its clinical significance (3).

Evolution of uniportal VATS

In the minds of many, a reduction in port or ports usually equate to limited access and maneuverability of the surgical instruments. However, since the emergence of uniportal VATS for major lung resection almost a decade ago, we have seen a rapid development in instruments and surgical technique (5). There is no doubt that evolution from triportal to uniportal requires the surgeon to adapt to new planes of visualisation and instrumentation (6,7). An understanding of the stepwise geometric basis of evolution of VATS approaches can help dispel misconceptions that visualisation and instrumentation is restricted when the converse may hold true (8,9).

In the triportal approach, the thoracoscope and rigid straight instruments are placed in a baseball diamond configuration corresponding to a rhombus, with the thoracoscope at home base, the hilum or target at second base, and instruments at first and third base. The three instruments are aimed towards the same vanishing point (10). The posterior port corresponding to first base is used for lung retraction and introduction of tissue staplers. The main issue with this approach is that instruments passed from the posterior port may interfere with the thoracoscope. In attempts to avoid the posterior instrument, the first assistant may drive the thoracoscope to an optical plane different from the instrumentation plane, presenting a perspective which hinders hand-eye coordination.

In the biportal approach, the posterior port is eliminated, and the anterior port is a utility mini-thoracotomy incision with passage of multiple instruments. This has a number of important implications for the surgeon. First, the plane of instrumentation is translated from a horizontal, caudocranial perspective to a vertical, anteroposterior perspective. Second, curved instruments may be required

in order to reach the whole thoracic cavity and to minimise fencing. Third, crossing manipulations are required to bring about effective traction-countertraction, and these maneuvers require transferring the effective fulcrum of instrumentation inside the chest cavity. Finally, the plane of instrumentation now runs perpendicular to the plane of visualization, hence could lead to more significant hand-eye inconsistency which may be difficult to overcome.

In the uniportal approach, the inferior thoracoscopy port is eliminated, and the anterior incision must now also encompass the thoracoscope. The plane of visualization is also translated to a vertical anteroposterior perspective, same as for the plane of instrumentation. The axes of thoracoscopic view and instrumentations thus become parallel. This simulates direct vision in a thoracotomy, and hand-eye inconsistency is minimized (8,9). It is interesting to note that it may be for this reason numerous centres have adopted the uniportal VATS approach directly from open surgery without transitioning through multiport VATS (11).

Metrics of oncological clearance in lung cancer surgery

Anatomical complete resection and mediastinal lymph node dissection that allow accurate pathological staging offers the best chance of cure for medically operable patients with resectable early-stage non-small cell lung cancer. The oncological clearance of lung cancer surgery very much hinges on the completeness of mediastinal lymph node staging. A point of contention for oncological clearance of any minimally invasive approach is whether differences in instrumentation and surgical technique hinders adequate nodal harvesting and thus the opportunity for nodal upstaging. With a reported incidence of nodal upstaging varying from 9% to 24%, a substantial portion of patients with pathological node-positive disease may benefit from adjuvant therapy if they are not understaged by suboptimal lymph node harvesting (12).

There is no consensus on the definition of a complete mediastinal lymph node staging. The 2019 National Comprehensive Cancer Network (NCCN) guidelines recommend either sampling at least three N2 stations or complete lymphadenectomy. Although mediastinal lymphadenectomy can theoretically identify more skip metastatic lesions and occult lymph node metastases, whether it leads to improved survival remains controversial (13).

In a 2017 analysis of large-scale Chinese and US multi-

institutional databases, a greater number of examined lymph nodes positively correlated with more stage migration and better overall survival in patients with node-negative disease. The cutoff was calculated to be sixteen examined nodes (14). To implement this metric in practice, surgeons should adhere to a stringent protocol for intraoperative nomenclature and enumeration of lymph nodes, as fragmentation may over-estimate the number of nodes harvested (15). This cutoff may allow for an additional metric for a more confident declaration of pathological node-negative disease, and could give the surgeon and the patient greater reassurance.

Is uVATS oncologically equivalent to mVATS?

To ascertain the state of the evidence regarding oncological efficacy of uVATS, the authors searched Medline and EMBASE using the strategy listed in the International Society for Minimally Invasive Cardiac Surgery (ISMICS) expert consensus statement on “Optimal Approach to Lobectomy for Non-Small Cell Lung Cancer: Systematic Review and Meta-Analysis” (16).

From January 2000 to October 2019, twenty-three articles comparing mVATS and uVATS were identified. Two studies were excluded from the current discussion because they did not report any oncological outcomes. The twenty-one remaining studies, involving 3,737 mVATS patients and 2,165 uVATS patients in total, were all retrospective in nature (10,17-36). Propensity score matching was performed in ten studies. Except for one conference abstract, the other articles were published in peer-reviewed journals. Characteristics of the included studies are listed in *Table 1*.

Sixteen studies reported the rate of early postoperative complications. However, there was significant heterogeneity in how complications were defined and classified. Overall, there was no significant difference in complications between the two groups. Bourdages-Pageau *et al.* reported less pneumonia in the uVATS group than mVATS, but the cause of this observation is unclear.

Eighteen studies compared the number of dissected lymph nodes harvested. Radiological nodal staging was often only partially reported or not reported at all. Routine lymphadenectomy was performed in thirteen studies, lymph node sampling in two studies, and in three studies the strategy is unclear. None of the articles defined the boundaries of lymph node stations or completeness of lymphadenectomy. Only one study reported the number

of lymph nodes harvested from N1 stations and N2 stations separately. All the studies showed that uVATS is non-inferior to mVATS in terms of number of lymph nodes stations sampled as well as number of lymph nodes harvested. Interestingly, the propensity matched study by Song *et al.* showed that the uVATS group had more lymph nodes harvested; however, the reason for this observation is unclear (32). Four articles reported the rate of pathological upstaging and no significant difference was found. Details on oncological outcomes of these eighteen studies are listed in *Table 2*.

Only two retrospective studies reported data on short- to mid-term survival. Han *et al.* from South Korea reported the results of 439 VATS lobectomies for stage I and II disease from 2006 to 2015, during the group’s transition from triportal to biportal and then to uniportal. The three-year overall survival was 87.3% for the triportal group (median follow-up of 75.7 months), compared with 93.7% for biportal (median follow-up of 56.5 months), and 93.2% for uniportal (median follow-up 27.5 months). There was no difference in both overall survival and disease-free survival between the three groups (22). Zhao *et al.* from China retrospectively reviewed results of 191 lobectomies performed on patients with T1a and T1b disease from 2013 to 2015. There was no difference in three-year overall survival between the thoracotomy group, multiportal group and uniportal group ($P=0.327$) (35). However, the exact percentage of surviving patients at three years in each group was not reported.

In 2014, our institution reported one of the first large-scale case series of uVATS lobectomies involving one-hundred thirty NSCLC patients. Despite the high prevalence of pulmonary tuberculosis in Asia, our experience is that the uVATS approach was not hindered by the presence of anthracotic hilar lymph nodes or dense pleural adhesions, as evidenced by a low conversion rate of 5.3% (2). The two-year overall disease-free survival rate was 96% for stage I disease and 83% for stage II and above, which was in line with these two studies.

Finally, the elephant in the room must be addressed. None of the studies explained the rationale behind the choice of VATS approach. The choice was largely a matter of surgeon’s discretion. One article frankly stated that “*the selection criteria between single-port and triple-ports were not special or different*” (36). Even with propensity score matching, the risk of selection bias was deemed to be high because only three out of ten studies reported the parameters incorporated in propensity score calculation.

Table 1 Studies included in analysis

| Author | Country/ region of origin | Year of conduct | Year of publication | Study design | Preoperative stage | Lung resection | Postoperative complications |
|---------------------------|------------------------------|--------------------|------------------------|-----------------|---|---|----------------------------------|
| Bourdages- Pageau (17) | Canada | 2014–2017 | 2020 | PSM | I and II, no further subgroup analysis | 722 lobectomies | Less pneumonia in uVATS group |
| Chang (10) | Taiwan | 2012–2014 | 2016 | Unmatched | Not reported | 100 lobectomies, 82.6% of included patients (segmentectomies included in analysis) | No difference |
| Chung (18) | South Korea | 2013–2014 | 2015 | Unmatched | Subgroup analysis of stage I available | 99 lobectomies | No difference |
| Dai (19) | China | 2013–2015 | 2016 | PSM | I to IIIA, no subgroup analysis | 143 lobectomies, 63 pairs propensity matched | No difference |
| Erşen (20) | Turkey | 2010–2016 | 2018 | Unmatched | I to IV (67% stage I), no subgroup analysis | 92 lobectomies | No difference |
| French (21) | Canada | 2014–2015 | 2016 | Unmatched | I to IIIA, no subgroup analysis | 82 lobectomies | No difference |
| Han (22) | South Korea | 2006–2015 | 2017 | Unmatched | I and II, no subgroup analysis | 439 lobectomies | No difference |
| Heo (23) | South Korea | 2012–2015 | 2017 | PSM | I to IIIA, including single station N2 disease | 104 lobectomies, 32 pairs propensity matched | No difference |
| Hirai (24) | Japan | 2011–2014 | 2016 | Unmatched | I | 80 lobectomies | No difference |
| Ke (25) | China | 2014–2016 | 2017 | PSM | T1a-c | 162 lobectomies | No difference |
| Kim* (26) | South Korea | 2006–2015 | 2017 | PSM | N/A | 241 lobectomies, 76 pairs propensity matched | Not reported |
| Li (27) | China | 2015–2017 | 2019 | PSM | N/A | 861 lobectomies, 246 pairs propensity matched | No difference |
| Lin (28) | China | 2013–2014 | 2016 | Unmatched | N/A | 67 lobectomies | Not reported |
| Liu (29) | Taiwan | 2005–2014 | 2016 | Unmatched | 60% stage I | 442 lobectomies | No difference |
| Mu (30) | China | 2014–2015 | 2015 | PSM | 90% stage I | 403 lobectomies, 47 pairs propensity matched | No difference |
| Shen (31) | China | 2013–2014 | 2016 | PSM | T1-3cN0 | 411 lobectomies, 100 pairs propensity matched | No difference |
| Song (32) | South Korea | 2011–2016 | 2017 | PSM | N/A | 63 lobectomies, 26 pairs propensity matched | No difference |
| Tosi (33) | Italy | 2014–2017 | 2019 | Unmatched | I-II | 1,980 lobectomies | No difference |
| Wang (34) | Taiwan | 2005–2013 | 2015 | PSM | N1 and single station N2 also included | 195 lobectomies, 46 pairs propensity matched, segmentectomy included in analysis | No difference |
| Zhao (35) | China | 2013–2015 | 2019 | Unmatched | I only | 191 lobectomies, open vs. mVATS vs. uVATS | No difference |
| Zhu (36) | China | 2014 | 2015 | Unmatched | I and II, no subgroup analysis | 82 lobectomies | No difference |

* , abstract. PSM, propensity score matched; uVATS, uniportal video-assisted thoracic surgery; mVATS, multiportal video-assisted thoracic surgery.

Table 2 Details on oncological outcomes

| Author | mVATS, n | uVATS, n | mVATS approach | Dissection or sampling | No. of LN stations sampled mVATS vs. uVATS | No. of LN sampled, mVATS vs. uVATS | Nodal upstaging, mVATS vs. uVATS |
|-------------|----------|----------|----------------|------------------------|--|--|----------------------------------|
| Chang (10) | 29 | 57 | 2-port only | Dissection | 4.5±1.2 vs. 4.4±1.3 (P=0.640) | 23.3±16.0 vs. 23.2±12.6 (P=0.983) | 17.5% vs. 23.1% (P=0.939) |
| Chung (18) | 39 | 60 | 3-port only | Unclear | N/A | 15.82±7.72 vs. 13.43±6.41 (P=0.202) | N/A |
| Dai (19) | 66 | 77 | 2-port only | Sampling | N/A | 17.9±6.7 vs. 17.0±6.1 | N/A |
| Erişen (20) | 81 | 21 | 2-3 ports | Dissection | N/A | N1: 8.7 vs. 10.3 (P=0.284); N2: 8.04 vs. 6.2 (P=0.401) | N/A |
| French (21) | 50 | 50 | 2-3 ports | Unclear | N/A | Same median no. of 7 (P=0.93) | N/A |
| Han (22) | 236 | 203 | 2-3 ports | Dissection | N/A | 3-port vs. 2-port vs. uVATS: 18±11 vs. 20±11 vs. 18±9 (log rank P=0.512) | N/A |
| Heo (23) | 37 | 67 | 2-3 ports | Dissection | 6 vs. 6 (P=0.09) | 28 vs. 25 (P=1) | N/A |
| Hirai (24) | 20 | 60 | 3-4 ports | Dissection | N/A | 12.8 vs. 13.6 (P=0.821) | N/A |
| Ke (25) | 97 | 65 | 3-port only | Sampling | N/A | 16±8 vs. 13±9 (P=0.882) | N/A |
| Kim (26) | 82 | 159 | N/A | Unclear | N/A | 19±11 vs. 17±10 (P=0.512) | N/A |
| Li (27) | 246 | 615 | 2-3 ports | Both | N/A | 15.3 vs. 15.6 (P=0.309) | N/A |
| Liu (29) | 342 | 100 | 2-3 ports | Dissection | N/A | 25.23±11.3 vs. 28.47±11.77 (P=0.013) | N/A |
| Mu (30) | 347 | 58 | 3-port only | Dissection | 5±1 vs. 5±2 (P=1.0) | 13.34 ± 9.26 vs. 7.02±8.60 (P<0.001) | N/A |
| Shen (31) | 115 | 296 | 3-port only | Dissection | N/A | 20.9±5.2 vs. 21.4±5.6 (P=0.54) | 43% vs. 38% (P=0.37) |
| Song (32) | 47 | 26 | 3-port only | Dissection | 2.8±1.2 vs. 3.6±1.2 (P=0.02) | 10.8±10.3 vs. 11.1±4.3 (P=0.889) | N/A |
| Tosi (33) | 1,808 | 172 | 2-3 ports | Dissection | N/A | Both groups with the same median of 12 (P=0.504) | 11.9% vs. 8.1% (P=0.172) |
| Wang (34) | 46 | 46 | 2-3 ports | Dissection | N/A | 25.19±11.41 vs. 27.30±12.21 (P=0.254) | N/A |
| Zhu (36) | 49 | 33 | 3-port only | Dissection | 4.4±0.8 vs. 4.4±1.0 (P=0.637) | 25.4±7.3 vs. 23.6±11.2 (P=0.737) | N/A |

uVATS, uniportal video-assisted thoracic surgery; mVATS, multiportal video-assisted thoracic surgery.

The effect of learning curve

Uniportal VATS is difficult to master. Dedicated and focused training is required at high-volume centres with close mentoring by experienced surgeons. Furthermore, surgeon and institutional experience has been shown to affect oncological clearance. An audit of five-hundred consecutive VATS lobectomies at New York-Presbyterian Hospital showed that significantly more lymph nodes were harvested in the latter half of the cohort. Further analysis of the learning curve of an individual surgeon in VATS lymphadenectomy showed that a plateau in the number of lymph nodes harvested was reached after the initial fifty cases (37). Gonzalez *et al.* analysed their initial three years of experience with VATS lobectomies at Coruna, during the group's transition from triportal to biportal. Two-hundred cases from 2007 to 2010 were divided into three cohorts by year and with increased experience, each year saw an improvement in nodal harvesting (38).

Although mVATS is the approach adopted in both studies, the results can be extrapolated to uVATS. Zhongshan University analysed the learning curve of the first one-hundred and twenty uVATS lobectomies performed by a group of experienced mVATS surgeons from 2013 to 2014 (39). The skin-to-skin time reached a plateau after the first thirty cases. Furthermore, there were significantly more conversions and unsuccessful attempts at passing the stapler in the first quartile of the cohort. Our own experience is that trainees should gain experience with biportal instrumentation first before transitioning to uniportal. In the event of technical difficulties, conversion to biportal approach can in most cases ensure safe and expedient conduct of the operation, by allowing more instruments to be introduced into the operating field, reduce instrument fencing and increase stapling angles.

Conclusions

Although there are no limitations intrinsic to the uniportal approach that compromises oncological efficacy, the use of uVATS for lung cancer remains controversial. Retrospective comparative studies suggest that oncological clearance of uVATS is equivalent to mVATS in terms of nodal staging and early mid-term survival, but their results should be interpreted with caution because of selection bias and lack of long-term follow-up. We echo Dr. Gonzalez-Rivas' call for more high-quality research in this arena, in order to ascertain the true value of uVATS in the armamentarium of

modern minimally invasive thoracic surgery (40).

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