Editorial

# One, two, three or four ports… does it matter? Priorities in lung cancer surgery

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Lung cancer surgeons can choose from an arsenal of techniques when offering minimal invasive surgery to their patients. These can be classified by the primary vantage point, the use of a robot, the use of a utility-incision (*vs*. total thoracoscopic), the location of the extraction point, the sequence of transection (hilum-first *vs*. fissure-first), the size of the ports or the number of ports. Combinations are possible and this results in a wealth of techniques. Obviously, surgeons with—sometimes without—experience like their own technique and tend to defend them. Some techniques are positioned as 'ultra-minimal invasive' such as uniportal surgery, micro-lobectomy (5 mm instruments and subxyphoidal extraction) or complete subxyphoidal resections. Subjectively, the clinical importance might make sense. But, hard objective data are missing to date.

Retrospective studies in general, including meta-analysis based on retrospective studies, should be interpreted with care as bias can often be identified. Even studies based on propensity score matching can draw false conclusions if key parameters are missing. Well powered prospective randomized trials are ideal to filter out random fluctuation. Even then, some bias can sneak in. Because of its particular nature, it is difficult to make studies concerning type of incision 'double-blind'. Therefore, the chosen technique can have an effect on patient and staff's expectations and treatment during the postoperative course. This might have an effect in favor of the 'least invasive' technique.

A prospective randomized study between 'uniportal' (n=51) and 'multiportal' (n=55) video-assisted thoracoscopic surgery (VATS) lobectomies was recently published in the EJCTS. Perna *et al*. found no differences in postoperative pain measured by the visual analogue scores (VAS), morphine use, time to remove the paravertebral catheter, chest drain, complications and duration of hospital stay. Age, clinical stage and comorbidity were comparable between the two groups. The authors concluded that uniportal lobectomy does not achieve better postoperative outcomes than other VATS techniques (1).

As mentioned by the authors and in the accompanying editorial, a point of attention in this study is the grouping of the 'two-port' technique with the 'three-port' technique because of problems with sample size (1,2). The adopted 'two-port' Duke technique can be regarded as a uniportal technique with a camera port in the same intercostal space near the 'utility port'. The fact that almost halve of the patients in the 'multiport' group were operated by this 'two-port' technique can be questioned. Possibly, it favors the 'multiport' group.

Many reports of negative RCT's (showing no statistical difference) are underpowered. They cannot state that clinically important differences are not present (type II error) (3). In this paper, a sample size was chosen to reach a statistical power of 80% to detect an expected difference in postoperative pain of two points on the VAS score. The power is the probability that you will detect a difference assuming that a true difference of a specific magnitude

exists. If the true difference is at least two points in VAS score, the chance that the negative finding (i.e., no significant difference in pain between the multiport and single port) is false is still 20%. It is regretful that for none of the outcomes confidence intervals (CIs) were reported. This is absolutely required when drawing conclusions about equivalence between groups. A CI for the difference in the location of a skewed distribution (such as the VAS score) can be obtained using the Hodges-Lehman estimator (reflecting the median difference in score between both groups). Strong claims about equivalence between groups are not appropriate when wide CIs are obtained. Not only the sample size of the study but also the variability of the VAS score determines the width of the CI. However, no information on variability is reported and graphs which allow appreciating whether the distribution of the score is truly comparable between groups are lacking.

Instead of reporting the CIs, the authors focused on non-significant P values. To be clear, one should not use a P value as an indicator of strength of pain relief. Very large studies can yield small P values while the effect—reduction of pain—is minimal and therefore not clinically important (4). Only the size of the values within the 95% CI will tell you if the effect is clinically important.

In addition, if the mean VAS scores are low in both groups (in this case around 3), the clinical relevance of a small difference is even more suspect (5). CIs are particularly interesting in small sample studies with negative results (P>0.05). A VAS score lower than three is generally accepted to be an analgesic success (6). If in one group, all scores are below 3 and in the other not, this can be still be useful information (6). Grouping patients (e.g., VAS <3, 3–7, >7), looking at the proportion of patients reaching a VAS score of less than 3 and exact dose of morphine usage might be a better outcome parameter (5,7). But even then, if a slightly higher dose of morphine is needed to achieve a similar comfort, the question of clinical importance remains.

Lancet Oncology recently published a randomized controlled trial between VATS (n=102) and anterolateral thoracotomy (n=99). With 206 patients needed, the study was designed to detect a difference of 20% in patients with moderate to severe pain with a power of 80%. The proportion of patients with clinically important pain (score ≥3) was significant lower after VATS in the first day after surgery (VATS 38%; 95% CI: 28–48 *vs.* thoracotomy 63%; 95% CI: 52–72, P=0.0012).

The ongoing UK multicentric VIOLET randomized controlled trial will also compare VATS and open surgery. The chosen outcome parameter is the self-reported physical function one month after surgery. The investigators calculated that 398 patients are needed to provide a 90% power, assuming that an effect size of 0.25 standard deviations in physical function would be clinically important. They also calculated that to detect a 1-day difference in hospital stay with a power of 80%, 498 patients are needed (8).

It can be assumed that the observed difference in outcome (both pain and physical function) will be smaller when investigating two minimally invasive techniques instead of open surgery *vs.* VATS. Only trials with more patients then above could detect it. And so, the question remains: does it matter how many ports the surgeon uses? Do we need a large randomized trial comparing uniportal with multiportal VATS resections? More important, will the possible statistically significant difference be clinically important? It seems that the surgical community should focus on other priorities first. If not, the respiratory oncologist or radiotherapist will.

## Priority I: promote safe surgery

Detection of a small increase of major complications by either technique seems to be more clinically important than a small difference in postoperative VAS score, if existent. Retrospective studies tend to underestimate vascular injuries. Major catastrophes with emergency conversions or pneumonectomies are often not captured in large databases (9). Incidence of major intraoperative complications during VATS anatomical resections was 1.5% in a retrospective European study with 3,076 patients intended to be treated by VATS (9). There is no indication in current literature that a uniportal technique is less safe. To detect a relative increase of 20% (1.8% *vs.* 1.5%) in incidence of major preoperative complications, one has to design an unrealistic trial with more than 75k patients (power 90%, alpha 0.05). Even then, results should be interpreted with care as a higher complication rate by one technique does not always relate with higher mortality rate, as seen in recent study on robotic VATS resections (10). Advanced care in high volume centres offering a new technique might lead to improved strategies to avoid 'failure to rescue', i.e., avoidable deaths after occurrence of complications (10). Whatever technique is used, development of skills to identify, judge and prepare

 

well high-risk cases in combination with proper exposure, meticulous dissection and identification of hilar structures before transection is highly recommended (9).

## Priority II: stimulate oncologic quality of resection

While safe surgery and improved perioperative care promote short-term survival, the quality of the oncologic resection is related with long-term survival. Variation in quality of surgery is computed to have 2–3 times more impact on long-term survival compared to short-term survival (11,12). The surgical community should more than ever strive towards a broadening of the quality assurance in all hospitals offering lung cancer surgery. While it is near accepted that the quality of SABR is more or less consistent across centres, data suggest that results of surgery reported in voluntary societal databases differ with national databases and are not generalizable (13).

Whether the oncologic quality of the surgery is more related with the training, determination and skills of the surgeon than the chosen access is difficult to study. Ideally, the results of the average surgeon using the techniques under investigation should be part of comparative studies.

Of particular concern is the quality of lymph node assessment. Guidelines emphasize its importance, but in reality this is infrequently performed. In 2005, a large survey by the American College of Surgeons showed that only 42% of patients had any mediastinal node sampled during surgery (14). Similar, a report based on the US Surveillance, Epidemiology, and End Results (SEER) database confirmed that in a majority of pN0–1 NSCLC resections mediastinal lymph nodes were not investigated (15). To further investigate and promote the quality of lymphadenectomy, the surgical community should endorse the use of a checklist during lymphadenectomy, use uniformly definitions of lymph node dissection both in extent (nodal stations) as in description of technique (en-bloc, complete removal with or without fragmentation, sampling) and account for patient variability of lymph nodes (16-18). Studies should include the central location of the tumor as this can be a selection bias and a decisive for the finding of lower N1 upstaging after VATS resection compared to open surgery in several studies (19,20).

The surgical community should follow the example of radiotherapists incorporating imaging in large datasets and embrace 'Rapid Learning' methodology enabling data sharing without additional burden to health care professionals and without the need for individual patient data to leave the hospital, with the aim to develop prediction models, tailored cancer therapy including patient preferences in the decision making (21,22).

## Priority III: increase the adoption rate of minimally invasive surgery

In a publication based on the ESTS database, VATS was performed in less than 25% of cases in Europe in 2013 (23). As the database is largely voluntary, real numbers are probably lower. In the US, performance of VATS compared to open surgery has continued to rise between 2010 and 2014 but remains under 50% in a recent analysis of 'Premier' hospital data' (24). Blasberg *et al*. found surgeon training specialty and hospital volume to be strongly associated with VATS usage. After stratification for training and hospital volume, surgeon volume on its own was related with a significant increase in VATS adaptation. In the US, centralization of care seems to explain some of the regional differences in VATS adoption (24).

## Conclusions

The outcome parameters in the evaluation of different minimally invasive techniques will be similar to those used in the comparison between VATS and open surgery. Similar warnings on safety and questions on complete resection will be made, while the relative gain in pain relief or self-reported physical function will be smaller. Possibly, the gain of 'ultra-minimal invasive' resections, is too small to be detectable in smaller studies, and too small to be clinically important in larger studies showing statistical significance.

Still, the discussion does matter. Surgeons can choose between techniques, allowing the resection they envisioned of similar oncologic quality as an open resection. The choice will depend on patient characteristics, but also resources, volume and surgeon's competence. The significance of the continuous debate lives in the opportunity to stress the priorities in lung cancer surgery: safety, complete resections with adequate lymph node dissection and the continuous quest towards higher adoption rate of minimal invasive techniques.

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## Footnote

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