Improving evidence for video-assisted thoracoscopic surgery lobectomy

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As thoracic surgeons, we strive to improve treatment with each procedure and aim at performing low-risk operations with an optimal oncologic outcome. Although the number of randomized controlled trials (RCTs) in thoracic surgery has increased, there are still relatively few RCTs published within the field and much of the existing evidence is based on retrospective studies (1).

In a recent RCT by Bendixen *et al.* (2) muscle-sparing anterolateral thoracotomy is compared with video-assisted thoracoscopic surgery (VATS) on post-operative pain and quality of life (QoL) after lobectomy for early stage lung cancer. During a 6-year period the authors included 206 patients in total, of whom 201 were included for final analysis, keeping staff and patients blinded to the procedure throughout hospital admission using identical surgical dressings. Post-operative pain was measured using numeric rating scale (NRS) six times daily during admission and 2, 4, 8, 12, 26 and 52 weeks after discharge. QoL was measured using EuroQol 5 Dimensions (EQ5D) and the European Organisation for Research and Treatment of Cancer 30-item QoL Questionnaire (EORTC QLQ-C30) daily during admission and at the same time intervals post-discharge. Data were analysed according to a modification of the intention-to-treat principle, where authors excluded five patients who did not have non-small-cell lung cancer. Accordingly one crossover patient in the VATS group due to conversion was kept in the original group for analysis. Briefly, the authors demonstrated improved outcomes in the VATS-group, including fewer patients with moderate-to-severe pain 24 hours post-operatively (P=0.0012) and at 1-year follow-up (P<0.0001) defined as NRS ≥3, and better QoL according to mean scores of EQ5D during the entire follow-up period (P=0.014).

QoL measurements and other patient reported outcome measures (PROMs) have gained increasing interest in thoracic surgery during the last decade, in parallel with other surgical specialties. Especially QoL is an important measure when evaluating treatment of this disease group, characterized by high risk of recurrence even after complete resection and low survival (3). Thus, PROMs play an increasing role in patient-centered care, and valuable data from this study can help align patient's expectations with the anticipated outcome, leading to improved treatment satisfaction. The authors have selected relevant QoL measurement scales. The EORTC QLQ-C30, employs an oncology-specific combination of several scales: function (physical, role, cognitive, emotional and social), symptom (fatigue, pain, nausea, vomiting, dyspnoea, insomnia, appetite, constipation, diarrhoea and financial difficulties), global health and QoL, and has been described according to required methodologic standards (4). The EQ5D scores mobility, self-care, main activity, social relationships, pain, mood and general health state, as a generic score which

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can be incorporated into quality-adjusted life year (QALY) calculations in health economics evaluations (5). Although Bendixen *et al.* used sound methodology in reporting QoL (6), they face known issues of PROMs namely response-bias with 67% of 1,388 questionnaires returned, among which 89% were complete, totalling in 60% of all.

To this date only three other RCTs comparing VATS with thoracotomy have been published in the English literature (7-9). While the studies documented a reduction in surgical complications (7), non-inferiority of overall 5-year mortality (8), and reduced inflammatory response (9) after VATS, none of the studies examined post-operative pain and QoL. Furthermore, the studies consisted of small sample sizes and were performed in the early years of VATS surgery and may therefore have limited applicability. Two Chinese RCTs published in 2007 compared QoL and post-operative serum cytokine levels after lobectomy by thoracotomy or VATS, and reported better QoL using the Lung Cancer Symptom Scale and similar cytokine levels in the VATS group (10,11). The studies, however, seem to report on the same patient population and consist of very small sample sizes, and could benefit the medical community by being translated to English.

Although VATS lobectomy has been performed since the 1990's, this minimally invasive technique has seen relatively slow adoption within thoracic surgical centres. In contrast, laparoscopic cholecystectomy underwent a short transition from the initial procedures to general consensus of adopting the technique as a new standard without solid evidence of the procedure's benefits (12). One of the greatest contributions to a fast-track surgical pathway within thoracic surgery came when VATS was introduced, however, more than two decades after the first procedure, high-level evidence of pain reduction and improved QoL were still lacking. This highlights the important contribution the study by Bendixen *et al.* has made. Furthermore, looking at the time of publication of the previous three RCTs (1995, 2000 and 2001), VATS surgery has undergone a tremendous evolution secondary to the improvements in the quality of the endoscopic equipment, staplers, energy devices and instruments over time. A report by the CALGB Surgery Committee in 2009 marked a new set of definitions for VATS lobectomies, in an attempt to eliminate traditions from open surgery such as the use of rib-spreaders and employment of the surgical incision to visualize the surgical field (13). These definitions were further modified and cemented in a consensus statement by an expert panel in 2014 (14). The differences between VATS and thoracotomy therefore may have been blurred by a high degree of heterogeneity in the early days of VATS. The surgical team behind Bendixen *et al.*, however, employed a widely accepted thoracoscopic technique of four ports, and furthermore used a muscle-sparing anterolateral approach to the open procedures, commonly accepted as the lesser invasive variant of thoracotomy.

Comparing open and thoracoscopic lobectomy not only serves as an important milestone in the modern age of thoracic surgery. It also gives credibility to the discussion of which VATS technique (uniportal, multi-portal or robotic) to prefer, now that there is solid evidence to the employment of a minimally invasive approach. Furthermore, previous and ongoing studies on surgical and post-operative management pain, morbidity and QoL may further improve by minimizing the surgical trauma using a fast-track approach (15,16).

There are still several areas that need further investigation, when comparing VATS with open thoracotomy, including cost-effectiveness and long term outcome of hard endpoints such as oncologic and all-cause mortality. Furthermore, as new treatment alternatives for early stage NSCLC emerge such as stereotactic ablative radiotherapy (SABR), surgical treatment must continually evolve to accommodate the increasing demands from patients and doctors. Results in the trial by Bendixen *et al.* need to be confirmed by new trials and systematic review and meta-analyses. A multicentre trial in the United Kingdom, led by Dr. Eric Lim (The VIOLET trial) is currently recruiting patients to compare cost-effectiveness and morbidity of VATS versus open thoracotomy with expected finalization in 2019 (http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-comparing-keyhole-surgery-with-open-surgery-for-people-with-lung-cancer-violet#undefined).

These studies remind us of the importance of continually generating and testing hypotheses in parallel with surgical and technical evolution to continually document the effects on morbidity and mortality. Luckily for the thoracic surgical community, results of coming trials together with follow-up data on the cohort in this recent Danish study will shed further light on the evidence behind VATS.

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Footnote

Conflicts of Interest: Henrik J. Hansen is the speaker for Medtronic, Bard, Medela; Rene H. Petersen is the speaker for Medtronic, Ethicon, Medela; Bo L. Holbek and Henrik Kehlet have no conflicts of interest to declare.

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