CONSENSUS STATEMENT

Video-Assisted Thoracic Surgery for Lung Cancer Resection
A Consensus Statement of the International Society of Minimally Invasive Cardiothoracic Surgery (ISMICS) 2007

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Objective: The purpose of this consensus conference was to determine whether video-assisted thoracic surgery (VATS) improves clinical and resource outcomes compared with conventional thoracotomy (OPEN) in adults undergoing lobectomy for lung cancer, and to outline evidence-based recommendations for the use of VATS in performing lobectomy for lung cancer.

Methods: Before the consensus conference, the best available evidence was reviewed in that systematic reviews, randomized trials, and nonrandomized trials were considered in descending order of validity and importance. At the consensus conference, evidence-based statements were created, and consensus processes were used to determine the ensuing recommendations. The American Heart Association/American College of Cardiology system was used to label the level of evidence and class of recommendation.

Results and Recommendations: The consensus panel agreed upon the following statements and recommendations in patients with clinical stage I nonsmall cell lung cancer undergoing lung lobectomy:

1. VATS can be recommended to reduce overall postoperative complications (class IIa, level A evidence).
2. VATS can be recommended to reduce pain and overall functionality over the short term (class IIa, level B evidence).
3. VATS can be recommended to improve delivery of adjuvant chemotherapy delivery (class IIa, level B evidence).
4. VATS can be recommended for lobectomy in clinical stage I and II non-small cell lung cancer patients, with no proven difference in stage-specific 5-year survival compared with open thoracotomy (class IIb, level B evidence).

Key Words: Consensus statement, Video thoracoscopic surgery, VATS, Lung cancer, Lobectomy.

Since the late 1980s, there has been an increasing interest in minimally invasive surgical techniques as smaller incisions hold the promise of less pain and earlier return to preoperative functional status.[1,2] Improved video-assisted visualization and associated equipment have allowed the performance of complex endoscopic thoracic surgical techniques, such as lung cancer lobectomy. Potential benefits of a lobectomy performed with minimally invasive techniques include reduced pain, reduced length of stay, along with improved cosmetic results and patient satisfaction, improved delivery of multimodality therapy, and improved long-term survival from cancer.[3]

Although the ability to perform major pulmonary resection using video-assisted thoracic surgery (VATS) has been available to thoracic surgeons for a number of years, the assimilation into practice has been only modest and inconsistent across regions.[4,5] Minimally invasive procedures remain controversial largely because of concerns of compromised long-term oncologic outcomes compared with thoracotomy. A prior systematic review[6] and other more recent studies suggested overall benefits from video-

assisted thoracic surgical procedures for selected pulmonary conditions, including pneumothorax and various lung resections.[6,7] Given the numerous recent publications and the technical evolution of the video-assisted procedures worldwide, a consensus conference was organized to systematically evaluate the relative advantages and disadvantages of VATS and OPEN lobectomy based on best currently available evidence.

METHODS

Purpose of the Consensus Conference

A consensus conference was held to clarify the safety and efficacy of VATS relative to conventional open thoracotomy (OPEN) in adults undergoing lobectomy for lung cancer. The primary objective was a careful evaluation of the evidence for relative merits and risks of VATS versus OPEN lobectomy to inform recommendations. The secondary objective was to identify the gaps in the needed evidence and to suggest a future research agenda.

Funding

Support for this consensus conference was provided by the International Society for Minimally Invasive Cardiothoracic Surgery (ISMICS), which has received unrestricted educational grants from industries that produce surgical technologies. Although ISMICS receives industry funding, no specific industry was linked with this consensus conference and support did not involve direct funding from manufacturers of devices related to VATS. Editorial independence was granted to the members of the expert panel, with the expectation that the resulting consensus statements would be clearly based on the best available evidence, identified by an explicit methodology to allow the reader/user to determine which aspects of VATS lobectomy were informed by evidence, and where evidence was lacking and opinion was required to create statements.

Selection of Panel Members

Members of the consensus panel were invited to participate by the chair (R.D.) and facilitator of the consensus process. Members included representation from four countries on three continents: six board-certified cardiothoracic surgeons, each with experience in both conventional and VATS, one cardiothoracic anesthesiologist/evidence-based researcher, and one methodologist with expertise in health technology assessment and meta-analysis. Four additional cardiothoracic surgeons who could not attend the conference participated in the development of the questions to be addressed in the literature review and the preparation of the manuscript.

Defining the Clinical Question

Before the consensus conference, the consensus panel was asked to define the clinical question, which involved defining the scope and depth of each of the following considerations: patient population of interest, intervention of interest, valid comparator group(s), and outcomes of interest.[8] The clinical question was developed collaboratively with input from all consensus panel members, and was finally stated as follows: "Does VATS improve clinical and resource outcomes compared with conventional thoracotomy (OPEN) in adults undergoing lobectomy as treatment for lung cancer resection? Specifically, does VATS compared with OPEN surgery improve:

1. Perioperative morbidity and mortality
2. Pain, functionality, and quality-of-life (QOL)
3. Perioperative resource utilization
4. Tumor staging, oncologic outcomes, and long term survival?"

Identifying Relevant Evidence

After the clinical questions had been defined, all published and unpublished evidence with acceptable study designs was sought to maximally inform this clinical question. Acceptable study designs included any randomized or nonrandomized comparative trial comparing VATS with OPEN in adults undergoing lobectomy for primary lung cancer. A full systematic review and meta-analysis of the evidence was performed before the conference. The complete methodology and results of the systematic review has been described in another article in this issue of *Innovations*.[9] In short, before the consensus conference comprehensive searches of Cochrane, Medline, EMBASE, and additional online databases[9] were conducted to identify all randomized and nonrandomized comparative trials of VATS versus OPEN for lung cancer that reported clinical- or resource-related outcomes. Potentially relevant trials were circulated to the consensus panel for review to determine agreement upon the inclusion criteria and whether any relevant trials were missed. Information related to baseline characteristics and outcomes was extracted independently by two authors (D.C., J.M.) from each study that met prospectively defined inclusion criteria. The appropriate data was synthesized by valid meta-analytic techniques to provide more precise aggregate outcome estimates. Trials that did not meet inclusion criteria were qualitatively summarized in tables to ensure all relevant data were addressed in the systematic review by the panel. The results of the systematic review and meta-analysis were used to populate evidence tables and graphs to form the basis for discussions and support the decision-making of the consensus panel. Comprehensive evidence for all potential benefits, risks, and resource considerations of VATS versus OPEN lobectomy was sought.

Reviewing and Presenting the Evidence

Before the consensus conference, each member of the consensus panel received a copy of the identified randomized and nonrandomized clinical trials and relevant background literature related to the clinical question. During the consensus conference meeting, the panelists were divided into groups and asked to address the following subquestions with the best available evidence from the meta-analysis:

1. Does VATS reduce perioperative morbidity (overall complications, arrhythmias, atelectasis, chylothorax, pneumonia, prolonged air leak, excessive blood loss, and transfusions) and mortality?

2. Does VATS reduce pain and improve functionality, satisfaction, and QOL?
3. Does VATS affect overall resource utilization (operating room time, length of stay, overall costs)?
4. Does VATS compromise the oncologic outcomes (ie tumor recurrence, tumor seeding, long-term survival)?

Applying the Evidence to Generate Recommendations

Levels of Evidence and Grade of Recommendations

The best evidence used to inform each clinical subquestion was classified according to the taxonomy suggested by American Heart Association/American College of Cardiology (AHA/ACC), as outlined in Table 1. This classification categorizes the evidence based on study design and susceptibility to bias, wherein higher levels of evidence and grades are labeled to highlight their lesser likelihood for bias and increased confidence in "closeness to the truth."[10–14] Several systems of grading recommendations and labeling strength of the evidence exist. The AHA/ACC system was chosen for consistency with other guidelines (http://www.acc.org/clinical/manual/manual_index.htm, accessed April 19, 2004) (Tables 1 and 2). As recommended by the guidelines, classification of the evidence and labeling recommendations is best done by the group panel using a democratic voting process after group discussion of the strength of the evidence.[15]

Members of the panel considered the highest possible level of evidence to inform their clinical subquestion, [eg, systematic reviews, meta-analyses, and randomized trials (RCTs) (level A evidence, Table 1) were considered superior

TABLE 1. Levels of Evidence

Level of evidence A
  Data derived from multiple randomized clinical trials
Level of evidence B
  Data derived from a single randomized trial, or nonrandomized studies
Level of evidence C
  Consensus opinion of experts

TABLE 2. Classes of Recommendations

Class I
  Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective
Class II
  Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
    IIa: Weight of evidence/opinion is in favor of usefulness/efficacy
    IIb: Usefulness/efficacy is less well established by evidence/opinion
Class III
  Conditions for which there is evidence and/or general agreement that the procedure/treatment is NOT useful/effective, and in some cases may be harmful

to nonrandomized clinical trials]. If there was insufficient level A evidence to inform the question, members reviewed nonrandomized comparative trials (level B evidence, Table 1). Only when level A and level B evidence was not available were noncomparative trials consulted to inform decisions (level C evidence, not formally included in the systematic review) along with expert opinion. When evidence from published or unpublished clinical trials to address the question was nonexistent, the consensus panel members were consulted. In each case, the best available level of evidence was explicitly stated and interpreted in light of its methodologic strengths and weaknesses before a statement of recommendation was made. As in previous consensus conferences, it was agreed that recommendations with higher levels of evidence should be interpreted with more confidence than recommendations based on lower levels of evidence, and that recommendations should be explicitly classified as per the ACC/AHA system (Table 2). After this review, each subgroup prepared a proposed draft statement.

Consensus Process and the Role of Evidence Versus Opinion

After each subgroup presented a proposed draft statement for their assigned subquestions to the entire consensus panel for further discussion of the strength, consistency, and clinical significance of the evidence, revisions were made until there was final agreement on each consensus statement along with its assigned level of evidence and class of recommendation.

When limited evidence was found to inform a clinical subquestion, it was explicitly recognized that scientific information would need to be supplemented by the interpretations and opinions of the experts. Legitimate conflicts over values and interpretations were resolved by discussion. Therefore, the consensus was not always unanimous, but was always representative of the majority of panel members. This is particularly true for the subquestions informed only by lower levels of evidence and expert opinion, where controversy was not resolved by clear evidence.

After each subquestion had been addressed, the entire consensus panel reviewed all of the recommendations to answer the overarching clinical question: Does VATS compared with OPEN lobectomy improve clinical and resource outcomes?

In summary, this consensus process sought to be primarily evidence-based, while allowing for opinions when the evidence was incomplete, and requiring that the basis for the statement be labeled by a declarative level of evidence. Bringing selected experts together in a consensus process allowed for breadth of perspectives and representation of interpretations for a multidimensional and carefully considered judgment of the evidence along with its certainties and uncertainties.

RESULTS

Included Evidence

Because no recent comprehensive systematic reviews were found at the time of this consensus conference, a

systematic review and meta-analysis of the randomized and nonrandomized evidence was performed before the conference by the authors[9] and was the basis for the formation of the recommendations. The systematic review of trials comparing VATS and open lobectomy for nonsmall cell lung cancer (NSCLC) with meta-analysis identified three RCTs (205 patients) and 33 non-RCTs (3384 patients) for a total of 36 trials involving 3589 patients. In addition, one additional RCT was included in the secondary analysis of complete- versus assisted-VATS (C-VATS vs. A-VATS).[9]

Case series and noncomparative trials (ie, VATS studies without an OPEN lobectomy arm, such as the recent CALGB feasibility trial) were excluded from this analysis.

Most trials identified were published in English (three were published in Japanese) after the year 2000, and were from a variety of countries including the United Kingdom, Japan, and United States.

Baseline Characteristics

The average age of patients at baseline was 65 years, approximately 60% of whom were male. On average, 6% of patients required conversion from planned VATS to OPEN. Most trials intended to include primarily patients with clinical stage I primary NSCLC. In the meta-analysis of RCTs, baseline characteristics were similar for VATS and OPEN patients. However, in the meta-analysis of non-RCTs, the baseline characteristics were different for gender, tumor size, histologic type, and pathologic stage, favoring VATS (Table 3). VATS patients were more likely to be women and have adenocarcinoma of smaller size and earlier pathologic stage than OPEN patients. Overall, in the non-RCTs, baseline prognosis was more favorable for VATS than for OPEN patients, limiting the interpretation of the clinical outcomes data from these trials.

Heterogeneity

For a number of outcomes, heterogeneity across studies was observed in the meta-analysis. Nevertheless, as much of the heterogeneity was driven by uncertainty about the size of effect and not the direction of effect, when detected it did not generally put into question the presence of significant benefit (with the exception of postoperative arrhythmias). Random effects statistical analysis was used to account for the heterogeneity found between trials for these outcomes.

TABLE 3. Baseline Characteristics: Level A and B

	VATS	OPEN	*P*
Stage I (%)	81.1	74.3	<0.0001
Stage II (%)	8.9	10.1	0.01
Stage III (%)	7.4	14.5	<0.0001
Stage IV (%)	2.9	1.5	0.35
Adenocarcinoma (%)	68.4	57.6	<0.0001
Squamous (%)	19.0	28.5	<0.0001
Other CA (%)	9.8	13.6	<0.0001
Tumor size (cm)	2.6 (1.3)	3.0 (1.6)	<0.004

Assigning Level of Evidence and Strength of Recommendation

The discussion and resulting evidence-based statements with assignment of levels of evidence and class of recommendation are given below for each clinical subquestion, and for the overarching clinical question. The aggregate results for RCTs (level A) from the meta-analysis are preferentially reported here; however, when RCTs were unavailable, aggregate results from non-RCTs evidence (level B) will be reported. Readers may consult the original meta-analysis publication for comprehensive reporting of both randomized and non-RCTs for all endpoints.[9] For discrete outcomes, odds ratios (ORs) and their 95% confidence intervals (95% CI) are reported. For continuous outcomes, the weighted mean difference (WMD, 95% CI) or standardized mean difference (SMD, 95% CI) is reported.

Question 1: Does VATS Reduce Perioperative Morbidity and Mortality?

The relevant outcomes considered for this question included overall postoperative complications, arrhythmias, atelectasis, chylothorax, pneumonia, prolonged air leak, excessive blood loss, transfusion rate, and all-cause mortality. For the composite endpoint of postoperative complications, a total of two RCTs and 12 non-RCTs were identified. Definitions varied for the subcomponents of postoperative complications included in the overall composite outcome definition reported in each trial. However, there was no heterogeneity across trials for this outcome in the aggregate analysis. Overall, the risk of any postoperative complication was significantly reduced by 70% in the VATS group compared with OPEN (OR 0.30, 95% CI 0.32–0.70; two RCTs, level A). When complications were considered individually, only one complication was significantly reduced: pulmonary complications were significantly reduced by 61% (OR 0.39, 95% CI 0.21–0.73; 5 non-RCTs, level B). Other complications, including respiratory dysfunction (one RCT, two non-RCTs, level B), pneumonia (one RCT, nine non-RCTs, level B), chylothorax (four non-RCTs, level B), pyothorax (one non-RCT, level B), atelectasis (one non-RCT, level B), prolonged air leaks (>7 days) (one RCT; 11 non-RCTs, level B), arrhythmias (one RCT, six non-RCTs, level B), and cardiac complications (one non-RCT, level B) were not significantly reduced with VATS versus OPEN. None of the studies reported any cases of wound infections (zero events, two non-RCTs; level B).

Although volume of blood lost was significantly reduced with VATS versus OPEN (−80 mL, 95% CI −110 to −50 mL; 18 non-RCTs, level B), this was considered clinically nonsignificant because of the small volume difference. Furthermore, the more clinically relevant bleeding outcomes were not significantly reduced, including excessive blood loss (generally defined as >500 mL) (one RCT, three non-RCTs, level B), reexploration for bleeding (one non-RCT, level B), and number of patients transfused (one RCT, six non-RCTs, level B).

Mean volume of chest tube drainage (−106 mL, 95% CI −206 to −7 mL; three non-RCTs) and the number of days

of drainage were significantly reduced (WMD −1.0 days; 95% CI −1.6 to −0.3 days; one RCT, 16 non-RCTs, level B).

The risk of death during hospitalization or up to 30 days was reported in 21 trials, and was not significantly different for VATS versus OPEN when RCTs were considered alone (zero events in two RCTs; level A) or in combination with non-RCTs (OR 0.79, 95% CI 0.38–1.64; two RCTs, 19 non-RCTs, level B).

Statements

1. VATS is associated with a significantly lower incidence of overall postoperative complications compared with OPEN lobectomy (level A).
2. Operative mortality, cardiac complications, reintubation or prolonged ventilation, atelectasis or pneumonia, and prolonged air leak are not different for VATS when compared with OPEN lobectomy (level B).
3. VATS is associated with shortened duration of chest tube drainage (~1 day less) when compared with OPEN lobectomy (level B).
4. Transfusion rates do not differ between VATS and OPEN (level B).
5. There is an equally low incidence of wound infection between VATS or OPEN lobectomy (level B).

Recommendation

In clinical stage I, peripherally located NSCLC, VATS can be recommended as an alternative approach to OPEN lobectomy to reduce postoperative complications (class IIa, level A).

Question 2: Does VATS Reduce Pain and Improve Functionality, Satisfaction, and Quality-of-Life?

The outcomes considered relevant for this question included patient-reported pain, analgesic use, patient-reported satisfaction with surgery or functionality scales, and patient-reported quality of life scores.

The incidence of severe postoperative pain was reduced by 97%, but was reported in only one trial (OR 0.03, 95% CI 0.00–0.30; one non-RCT, level B). The incidence of "any" postoperative pain was not reduced (two non-RCTs; level B). The incidence of pain measured after discharge and up to 1 year was reduced by 75% (OR 0.25, 95% CI 0.10–0.60; two non-RCTs, level B), and incidence of postoperative pain measured after more than 1 year was reduced by 61% with VATS versus OPEN (OR 0.39, 95% CI 0.16–0.93; one RCT, three non-RCTs, Level B). Pain measured via the 10-point visual analog scale (VAS) was significantly reduced by less than 1 point on day 1 (two non-RCTs), by more than 2 points at 1 week (five non-RCTs), and by less than 1 point at week 2 to week 4 (three non-RCTs, level B). At 3 months to 3 years' follow-up, there was no different in VAS scores.

Analgesic requirements were also significantly reduced, whether measured by total dose requirements (SMD −4 units, 95% CI −7 to −1 units; three non-RCTs, level B), number of times analgesics were administered (WMD −four administrations, 95% CI −6 to −1 administrations; six non-

RCTs, level B), or duration of analgesic requirements (WMD −3 days, 95% CI −5 to −1 day; five non-RCTs, level B). Recurrent nerve palsy was not significantly reduced (two non-RCTs).

The incidence of patients who were discharged to home care or other dependent care was reduced by 85% (OR 0.15, 95% CI 0.04–0.52; one non-RCT; level B) and percent change in 6-minute walk distance was improved (WMD 17%, 95% CI 12%–22%; one non-RCT, level B) with VATS versus OPEN. The incidence of patients reporting limited activity at 3 months was reduced by 96% (OR 0.04, 95% CI 0.00–0.82; one non-RCT, level B) and time to full activity was reduced by 1.5 months (WMD −1.5 months, 95% CI −2.1 to −0.9 months; two non-RCTs, level B). Patient satisfaction and QOL scores generally did not differ between groups. Although some physical function subscores differed significantly over the short term and midterm (shoulder strength, arm/shoulder functionality scores), overall patient-reported physical function scores did not differ between groups at 3-year follow-up (one non-RCT, level B).

Percent change in postoperative vital capacity postoperatively (WMD 20%, 95% CI 14%–25%; one non-RCT, level B) and vital capacity at 1 year (WMD 7%, 95% CI 2%–12%; two non-RCTs, level B) were significantly greater for VATS versus OPEN surgery. However, other measures of pulmonary function (postoperative % predicted force expiratory volume in 1 second (FEV_1) vital capacity, Pa_{O_2}, Pa_{CO_2}) were not improved with VATS versus OPEN.

Statements

1. Less analgesia (total dosage, duration, total administrations) is required in hospital for VATS versus OPEN lobectomy (level B).
2. Postoperative pain measured by VAS is significantly reduced at 1 day, 1 week, and 1 month, but not at 3 months with VATS compared with OPEN lobectomy (level B).
3. Chronic pain and need for treatment greater than 1-year are significantly reduced with VATS compared with OPEN lobectomy (level B).
4. There is no difference in postoperative neuralgia between VATS and OPEN lobectomy (level B).
5. Multiple measures of function (including 6-minute walk test, dependent status at discharge, shoulder dysfunction, activity at 3 months, time to full activity) are improved with VATS compared with OPEN lobectomy (level B).
6. There is limited data available which suggests that pulmonary function may be better preserved with VATS over OPEN lobectomy (level B).

Recommendation

In clinical stage I, peripherally located NSCLC, VATS can be recommended as an alternative approach to OPEN lobectomy to reduce postoperative and long-term pain, and to better maintain overall function (class IIa, level B).

Question 3: When Compared With OPEN Lobectomy, Does VATS Affect Overall Resource Utilization?

The outcomes considered relevant for this question included length of stay, operation time, and overall costs. Overall, hospital length of stay was not significantly reduced when RCTs were considered alone (two RCTs, level A), but was reduced by 3 days for VATS versus OPEN when RCTs and non-RCTs were considered in aggregate (WMD -3 days, 95% CI -2 to -1 days; two RCTs, 17 non-RCTs; level B). Three days represented an approximately 20% reduction of length of stay in the OPEN surgery group, because patients stayed on average nearly 14 days in the OPEN group in these studies. Similarly, operative time was not significantly different when only RCTs were considered (two RCTs; level A), but was significantly increased by 16 minutes with VATS versus OPEN lobectomy when all trials were considered in aggregate (WMD 16 minutes; 95% CI 3–30 minutes; two RCTs, 23 non-RCTs, level B). Total costs associated with surgical procedure plus hospital stay was significantly increased for VATS versus OPEN patients in the aggregate analysis of two non-RCTs reporting costs (SMD 0.7 monetary units, 95% CI 0.2–1.2; 2 non-RCTs, level B). However, this is based on a SMD of two small studies that evaluated differences in costs retrospectively in two different countries with differing health care systems, and did not specify an algorithm for expedited discharge.

Statement

1. Length of hospital stay is not different for VATS compared with OPEN lobectomy in RCTs (level A), but is significantly reduced by 20% in non-RCTs (level B).
2. Operative time is not different for VATS compared with OPEN lobectomy in RCTs (level A), but is significantly prolonged by about 16 minutes in non-RCTs (level B).
3. There is insufficient evidence available to compare total costs between the two procedures (level B), and further study on the cost-effectiveness of VATS versus OPEN are required.

Recommendation

In clinical stage I, peripherally located NSCLC, VATS can be recommended as an alternative approach to OPEN lobectomy, but without proven reduction in resource utilization (class IIa, level B).

Question 4: When Compared With OPEN Lobectomy, Does VATS Compromise the Oncologic Outcomes Including Node Dissection, Local/Distal Recurrences, Time to Adjuvant Chemotherapy Treatment, and Long-Term Survival?

Relevant outcomes for this question included node dissections or sampling, cancer recurrences, adjuvant chemotherapy reductions or delays, and overall or stage-specific survival over the longer term.

The mean number of lymph nodes dissected or biopsied (WMD 0.2 nodes, 95% C1 -0.8 to $+0.5$ nodes; two RCTs, 12 non-RCTs, level A) as well as the number of lymph node stations sampled (WMD 0.6 stations, 95% C1 -0.3 to 1.5 stations; two non-RCTs, level B) was not significantly different between VATS and OPEN.

The incidence of cancer recurrence (whether local or distal) did not reach statistical significance between VATS versus OPEN, although the trend was toward reduced recurrence in the VATS group (OR 0.78, 95% CI 0.58–1.04; one RCT, six non-RCT, level B). When local recurrences were considered separately from distal recurrences, there was no significant difference between either type of recurrence, although the trend was toward reduced recurrence for VATS, whether local (one RCT, seven non-RCTs, level B) or distal (one RCT, five non-RCTs, level B).

Delays in planned adjuvant chemotherapy were significantly reduced by 85% for VATS versus OPEN (OR 0.15, 95% CI 0.06–0.38; one non-RCT; level B), and incidence of reduction in planned doses was also reduced by 63% (OR 0.37, 95% CI 0.16–0.87; one non-RCT; level B). The incidence of failure to receive at least 75% of planned chemotherapy without delay or reduction was reduced by 59% (OR 0.41, 95% CI 0.18–0.93; one non-RCT; level B).

Risk of death did not differ between groups at 1 year (five non-RCTs; level B), 2 years (one non-RCT, level B), and 3 years (one RCT, five non-RCTs; level B). However, mortality at 5 years was significantly reduced by 33% (OR 0.67, 95% CI 0.47–0.97; one RCT, seven non-RCTs, level B). Whether this is because of a true difference in survival attributable to VATS technique, or whether it is because of the baseline imbalance in prognostic factors remains to be defined (few RCTs reported deaths over the longer term), and the panel felt that it would be premature to conclude that VATS significantly improves 5-year survival at this time, although the hypothesis is important and should be the focus of future trials.

Survival rates for stage IA (OR 0.96, 95% CI 0.58–10.60; four non-RCTs, level B) and stage IB (OR 0.69, 95% CI 0.43–1.12; three non-RCTs, level B) did not differ when considered separately, or when both stages IA and IB were considered together (OR 0.85, 95% CI 0.61–1.19; nine non-RCTs; level B). One non-RCT reported death rates for stage II and stage III and found no significant difference (one non-RCT, level B).

Statement

1. Stations sampling/dissection appears to be comparable between VATS and OPEN lobectomy (level B).
2. The number of lymph nodes resected or counted appears to be similar between VATS and OPEN lobectomy (level A).
3. Delivery of planned adjuvant chemotherapy is more feasible after VATS than OPEN lobectomy (level B).
4. As measured by pathologic stage-specific 5-year survival, there is no proven difference in survival for VATS versus OPEN lobectomy (level B).

Recommendation

1. In clinical stage I, peripherally located NSCLC patients who are undergoing VATS lobectomy, it is not unreasonable to perform VATS to establish locoregional extent of disease (class IIb, level B).
2. In patients who would be considered for adjuvant therapy based on pathologic stage, VATS can be recommended to facilitate delivery of adjuvant chemotherapy (class IIa, level B).
3. VATS can be recommended as an approach to lobectomy in clinical stage I and II NSCLC, but with no proven difference in stage-specific 5-year survival (class IIb, level B).

DISCUSSION

From our review of the literature, this is the first consensus evaluation of the evidence for VATS on treatment for lung cancer lobectomy. A systematic approach to defining the research question, identifying all relevant published and unpublished evidence, and labeling that evidence basedd on its quality has been performed to produce statements that represent the best available guidance for evidence-based clinical practice and resource decisions. These statements should be interpreted and applied with full acknowledgment of the level of evidence that informs that statement, (eg statements based on level A evidence are given more confidence than those of level B or less).[11,16] Every effort was made throughout the consensus process and peer review process to ensure that the recommendations are clearly stated, and their basis clearly documented to prevent overstating of the evidence and simplistic interpretation of the statements.

Overall, the recommendations suggest that VATS may have advantages over thoracotomy with respect to reduced risk of perioperative complications, reduced postoperative pain, improved functionality, and improved delivery of adjuvant chemotherapy. Other evidence suggests that VATS may increase resource requirements; however, this evidence was preliminary and the trials failed to ensure that patients undergoing VATS lobectomy were assessed for "Fast-Track" discharge.[17] Valid economic analyses using contemporary VATS and OPEN techniques, and measuring all applicable resource utilization over the shorter and longer term are required before more definitive conclusions of relative cost-effectiveness can be given.

For other clinically relevant endpoints beyond those mentioned above, no difference was found for either technique. However, in most cases, there was a lack of sufficient power in the number and size of clinical trials reporting these outcomes to comfortably rule out the possibility of clinically important effect sizes, and one of the most important findings of this consensus conference is that additional randomized directly comparative trials are required to further delineate the role of VATS versus OPEN. Importantly, for none of the reported clinical endpoints was VATS found to be less favorable or more risky than OPEN lobectomy. However, the reliance on retrospective studies reduces the likelihood that complicated patients were uniformly included and accounted for in the analyses, and the overall results may be biased in favor of VATS if complicated patients crossed over to and were accounted for as OPEN lobectomy (Table 1 in the accompanying meta-analysis).[9]

Because few randomized comparative trials have been conducted comparing VATS versus OPEN, only one of our recommendations is based on level A evidence. The three existing RCTs of VATS versus OPEN surgery for lobectomy included only a total of 205 patients, and therefore, the lack of statistically significant differences found in RCTs may be because of the lack of adequate power. This conclusion is supported by the wide CIs shown for the effect estimates drawn from the RCTs in the meta-analysis. When non-RCTs were added into the meta-analysis, the power was increased and a number of significant differences were found. Nonetheless, the impact of baseline prognostic factor differences because of selection bias in these RCTs could not be adjusted for in this analysis, and the significant differences found must therefore be interpreted cautiously (ie with full acknowledgment that it is only level B evidence, and with interim application to decision making in anticipation that future RCTs may soon improve the evidence based). Respecting that decisions will have to be made before the evidence based addresses important gaps in our knowledge about VATS versus OPEN lobectomy, this consensus statement attempts to summarize the best available evidence so far, to assist clinical decision making until more definitive evidence becomes available. The most assured role for VATS at this time would be in a validly designed RCT compared with OPEN lobectomy, and this consensus statement should not be misinterpreted to suggest that such trials would be unethical. None of the most clinically relevant outcomes (ie long-term survival, cancer recurrence, long-term pain) has been proven to be better for VATS or OPEN, and RCTs are urged to address this equipoise. For those who do not have sufficient resources to perform RCTs, this consensus statement provides guidance for the role of VATS in practice for surgeons who are adequately skilled in the technique.

Complete (C-VATS) Versus Assisted (A-VATS) and Nonstandardized Definitions

The literature search found variation in the definitions of VATS to vary between the studies included (See Table 1 in the meta-analysis).[9] It was not possible to adopt a uniform definition for VATS for this consensus conference because a number of trials did not provide adequate information about the use of rib spreading, tissue retractors, incision size, and direct visualization to allow for subanalyses of outcomes by definition of VATS. Standardization of VATS definitions will be necessary before concerted progress can be made in this area (as suggested by CALGB 39802 Trial, where VATS was defined as a "true anatomic lobectomy with individual ligation of lobar vessels and bronchus as well as hilar lymph node dissection or sampling using the video screen for guidance, two or three ports, and no retractor use or rib spreading")[18] particularly if the use of rib spreaders, retractors, and large incisions has a significant impact on outcomes as suggested at least preliminarily by the evidence found in this meta-analysis.

This consensus conference did not specifically address definitions of VATS, and the relationship between differing aspects of VATS technique to measured outcomes. A preliminary exploration of the relationship between the degree of invasiveness of VATS and the reported outcomes was performed.[9] When patients undergoing lobectomy with C-VATS (completely endoscopic, without rib spreader) were compared with those undergoing A-VATS (usually with a rib spreader, through a minithoracotomy), there was a significant reduction in pain scores or duration of analgesia (SMD −0.7, 95% CI −1.0 to −0.4; one RCT, one non-RCT; level B), length of hospital stay (WMD −3.6 days, 95% CI −5.1 to −2.1 days; one RCT, one non-RCT; level B), duration of chest tube drainage (WMD −1.6 days, 95% CI −2.4 to −0.8 days, one RCT, one non-RCT; level B), and blood loss (WMD −45 mL, 95% CI −65 to −26 mL; one RCT, two non-RCTs; level B), but at the cost of increased OR time of 27 minutes (WMD 27 minutes; 95% CI 16–37 minutes; one RCT, two non-RCTs; level B). These results were corroborated by a subanalysis, whereby the results of the original meta-analysis were compared with the results after all studies using rib retractors (or unspecified) were excluded. The subanalysis showed that some (but not all) differences were more apparent when the analysis was limited to nonrib spreading VATS versus OPEN lobectomy. Overall, this provides support for the hypothesis that VATS without a rib spreader may have improved outcomes including reduced pain, chest tube drainage, blood loss, and hospital length of stay over more invasive VATS with minithoracotomy and rib spreader (level B). But, greater OR time may be required to perform less invasive VATS (level B). More research is encouraged to test this hypothesis prospectively.

Strengths and Limitations

This consensus statement is based on a current and comprehensive systematic review of the evidence, with formal explicit consensus processes that limited the role of opinion.

A notable strength of this consensus statement is its reliance on the evidence based, with comprehensive consideration of benefits, risks, and resource-related issues. The methodology undertaken and recommendations provided by this consensus conference are in agreement with current recommendations for developing consensus statements and guidelines.[15,16] To self-appraise our consensus statement against current standards for valid guidelines, we subjected our consensus process and recommendations to quality assessment checklists, and found that most indicators of quality were met or exceeded.[16,19,20]

Clinicians tend to overestimate the effectiveness of new interventions, especially if the intervention in question rests within the realm of their expertise, unless they objectively take into account a systematic review of the evidence.[21] There is a tendency for group decision-making processes to experience "regression to the mean" or a group-think effects, whereby compromises are made in recommendations to come closest to pleasing all members of the panel, even for issues that start off greatly polarized. To mitigate these risks, experts in evidence-based methodology and health technology as-

sessment from within and outside of the surgical field were invited to facilitate the discussion and to ensure the best available evidence was the focus for discussion rather than opinions or political charges. This process has been similar to other ISMICS consensus conferences conducted in recent years.[22–24]

Although international cardiothoracic surgeons and experts in evidence-based methodology and health technology assessment were represented on the consensus panel, some stakeholders were not represented. In particular, patients, administrators, and policy makers, were not invited to participate; however, patient-related outcomes including satisfaction and quality of life were sought from published trials to address this perspective. It is unfortunate that patient satisfaction was infrequently reported in the studies. In addition, stakeholders from the manufacturing sector (ie producers of technologies related to endoscopic and open surgery) were not included in the consensus and review process, to reduce the risk of bias that may result from direct manufacturer involvement.

A few important limitations in the current VATS literature were observed by the panel, and were carefully balanced when addressing the question if VATS improves clinical and resource utilizations in comparison with OPEN lobectomy:

1. There were baseline imbalances in patient gender, tumor size, pathologic stages, and histology in the non-RCTs. (Therefore, pathologic stage mortality was subanalyzed and reported rather than overall 5-year survival).
2. Variable definitions of VATS (ie some allowed soft tissue or rib spreading), size of thoracotomy incision, and an admixture of extent of resections such as wedge, segment, and lobectomy. (Therefore, this meta-analysis focused on VATS vs. OPEN lobectomy with less than 10% wedge resection. A subanalysis was also performed on C-VATS and A-VATS, as discussed in the previous section).
3. Inconsistent management of patients who crossed over from VATS to OPEN surgery because of aberrant anatomy, or intraoperative bleeding, and dropouts; and in most trials, patients who crossed over were either excluded or accounted for in the OPEN group. Studies that analyzed crossover patients may provide overestimations of benefit because the risk of crossover to OPEN surgery is not included in the VATS group. Of trials that reported crossovers, there was an average of 6% of patients who required conversion to OPEN surgery. The outcomes of patients who require conversion have not been separately reported, but are likely significantly greater than those who do not crossover. (Therefore, this meta-analysis represented those related to patients who undergo VATS without requiring crossover to OPEN lobectomy, and should be interpreted as such).
4. The lack of RCTs to inform every aspect of this consensus statement. Although this limitation is ubiquitous in medicine and is true of most, if not all, other con-

sensus statements,[15,25] it does not provide reason to abandon the consensus statement or afford it less credence. Rather, the purpose of evidence-based consensus statements is to explicitly define the best available evidence to inform each statement, in order that clinical and resource-related decision making can be optimally evidence based. Even without availability of an ideal evidence based, decisions must be made. Examination of the statements and their supporting levels of evidence outlines when greater assurance (level A) or lesser certainty (level B, and especially level C) can be given to the statement.

5. Low quality scores and lack of representation of patients with severely decreased lung capacity on published trials: although few trials explicitly included higher risk patients, it is unknown whether these results will apply to patients with more severely affected lung capacity, or with other high-risk characteristics.

As pointed out in the meta-analysis that underlies these evidence-based recommendations, most clinical trials of VATS versus OPEN lobectomy were nonrandomized. As a result, there will be inherent biases in the evidence. In particular, selection bias may increase the likelihood that patients with differing prognoses will be systematically chosen for VATS versus OPEN, and some of the differences favoring VATS found in the meta-analysis may be attributable to this selection bias. Because the influence of impact of this bias is not known, readers should bear in mind that the evidence based for statements labeled with level B may be an overestimation of the overall magnitude of benefit. The consensus panel incorporated this uncertainty into their discussions and assigned the class of recommendation to reflect this uncertainty.

Statement on Future Research

A number of gaps in the evidence were identified throughout the consensus process. Based on discussion of the limitations of the evidence based, the following areas were suggested by the consensus panel as priority areas for future research.

Trial Design

Future trials should be designed to maximize validity, with incorporation of valid randomization processes, and primary analysis by intention-to-treat, with subsequent subanalysis of patients who crossover. In addition, trials should be of adequate duration to measure the most clinically relevant outcome—long-term survival.

Definitions

Efforts should be made to standardize definitions of VATS. A variety of techniques have been used under the name of VATS, ranging from totally endoscopic lobectomy performed without rib spreading to minithoracotomy with the videoscope being used to illuminate the operative field for direct vision.

Outcomes

Because there is inadequate power in the existing small RCTs of VATS versus OPEN lobectomy, the majority of outcomes have not been adequately addressed. Although the balance of the evidence suggests there may be a possibility of improved survival and reduced risk of tumor recurrence, these are based on non-RCTs with measurable selection bias. Therefore, all clinically relevant outcomes remain to be proven in future adequately powered RCTs that control for selection biases. In particular, outcomes that should be given high priority in future RCTs include, long-term survival, tumor recurrence, short- and long-term pain, QOL, and overall resource utilization. In addition, studies are urgently needed to address all relevant clinical and resource outcomes for patients undergoing totally endoscopic lobectomy (complete VATS, C-VATS) versus partial endoscopic lobectomy (Assisted VATS, A-VATS). One previous RCT has studied A-VATS versus C-VATS, but it was underpowered to detect important differences. Head-to-head studies of varying degrees of invasiveness would help to define standards and consistent definitions for VATS.

Feasibility and Training

Judgments about whether the costs and uptake of VATS are feasible depend on the local context and setting. Feasibility issues worth considering include time, skills, staff, training and equipment necessary to carry out the recommendations, and the ability of systems of care to implement them. Administrative barriers to implementing these recommendations were not explicitly discussed during the consensus conference, because of the broad range of global contexts represented by the consensus panel. Issues to consider when localizing these recommendations to specific settings include skills development programs, supervising surgeons' expertise in VATS, availability of equipment, and supporting perioperative medical team. The learning curve for VATS is steep, and it should not be presumed that these evidence-based recommendations should be applied without consideration of individual skills development.

Future Directions

These consensus statements will need to be revisited and updated if there are changes in the available technologies, or significant evidence on the benefits and harms, and resource implications change. Research efforts should be encouraged to address the gaps in the evidence as outlined in the statement for further research given above.

Summary and Conclusions

After formulating each of the substatements for the four subquestions, the consensus panel discussed what should be the overall role of VATS compared with OPEN lobectomy in clinical practice in light of the current evidence based and its limitations.

For the primary question, "Does VATS compared with OPEN surgery in adults undergoing lobectomy for lung cancer improves clinical and resource outcomes?", the consensus panel recommended the following (Table 4): in patients with clinical stage I NSCLC, VATS can (the word

TABLE 4. Summary Consensus Recommendations for VATS Versus OPEN

Class of Recommendations and Level of Evidence	ISMICS Consensus Recommendations VATS Versus OPEN Lobectomy
Class IIa; level A	VATS can be recommended in patients with clinical stage I NSCLC to reduce overall postoperative complications
Class IIa; level B	VATS can be recommended in patients with clinical stage I NSCLC to reduce pain and overall functionality over the short term; and to improve adjunctive chemotherapy delivery
Class IIb; level B	VATS can be recommended for lobectomy in clinical stage I and II NSCLC patients with no proven difference in stage specific 5-yr survival

"can" is used rather than "should", to suggest that VATS remains an option to be selected, but the evidence is not strong enough to suggest that VATS should be mandated) be recommended:

1. To reduce overall postoperative complications (class IIa, level A evidence).
2. To reduce pain and overall functionality over the short term (class IIa, level B evidence).
3. To improve adjunctive chemotherapy delivery (class IIa, level B evidence).
4. For lobectomy in clinical stage I and II NSCLC patients, but with no proven difference in stage-specific 5-year survival (class IIb, level B evidence).

The panel also noted the lack of adequate RCTs to address this very important question. These statements are intended to guide practice until further evidence becomes available. Future clinical trials are strongly encouraged to allow for these recommendations to eventually be supported by level A evidence, with greater certainty of outcomes. Future clinical trials should be randomized controlled comparisons of VATS (eg, defined as per CALGB)[18] versus contemporary OPEN lobectomy, and should make every effort to ascertain all important outcomes (pain, neuropathy, analgesic requirements, return to full function, patient satisfaction, QOL, local and distal tumor recurrences, all-cause mortality, over the short and long term (ie over 5 years or more) with full follow-up of all patients.

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