Enhanced recovery after video-assisted thoracoscopic surgery lobectomy: a prospective, historically controlled, propensity-matched clinical study

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Background: Enhanced recovery pathways or fast-tracking following surgery can decrease the rate of postoperative complications and hospital length of stay. The objectives of this study were to implement an enhanced recovery after surgery (ERAS) pathway for patients undergoing a video-assisted thoracoscopic surgery (VATS) lobectomy, to assess the safety and efficiency of this protocol by measuring associated postoperative outcomes, and to compare the outcomes for patients in the ERAS group with the outcomes for patients in a propensity-matched control group.

Methods: The study was a prospective clinical trial. Patients who were scheduled to undergo VATS lobectomy at the Centre hospitalier de l’Université de Montréal in Montréal, Québec, Canada, were enrolled between November 2015 and October 2016. The ERAS pathway was used for all enrolled patients. The primary outcome was the number and severity of complications measured by the Comprehensive Complication Index. Secondary outcomes included length of stay, readmission and recovery. Recovery of patients was measured using EQ-5D-5L preoperatively and at 1 week, 1 month and 4 months after surgery. Prospectively enrolled patients were propensity matched to historical controls.

Results: Ninety-eight patients (36 men and 62 women) in the ERAS group and 98 patients in the control group (29 men and 69 women) were included in the analysis. The mean age was 65.2 ± 9.3 years, the mean body mass index (BMI) was 26.9 ± 5.9 kg/m² and the median Charlson Comorbidity Index score was 2 (interquartile range [IQR] 2–3) in the ERAS group. In the control group, the mean age was 66.2 ± 9.4 years, the mean BMI was 27.4 ± 5.6 kg/m² and the median Charlson Comorbidity Index score was 3 (IQR 2–3). A total of 23 patients (23.4%) in the ERAS group and 28 (28.6%) in the control group experienced 1 or more postoperative complications. The mean Comprehensive Complication Index score was 7.4 ± 16.8 in the ERAS group compared with 8.0 ± 14.3 in the control group (p = 0.79). The median postoperative length of stay was 3 days in the ERAS group and 5 days in the control group (p < 0.001). Five patients in the ERAS group and 4 patients in the control group were readmitted. The protocol adherence rate was 64.3%.

Conclusion: It is feasible to implement an enhanced recovery protocol after VATS lobectomy. Although the pathway is still early in its development in Canada, implementation of an ERAS pathway after VATS lobectomy was associated with decreased length of stay, with no observable increase in complication or readmission rates.

Clinical trial registration: ClinicalTrials.gov, no. NCT02584322

Contexte : Les protocoles de récupération optimisée, ou réhabilitation précoce, après une intervention chirurgicale permettent de réduire les taux de complications postopératoires et d’abréger le séjour hospitalier. Les objectifs de cette étude étaient d’appliquer les principes de récupération optimisée après une chirurgie (ou ERAS, enhanced recovery after surgery) à des patients soumis à une lobectomie par chirurgie thoracique vidéo-assistée (CTVA), d’évaluer l’innocuité et l’efficience d’un tel protocole en mesurant les paramètres postopératoires associés, et de comparer l’issue de l’intervention chez les patients du groupe ERAS à celle des patients d’un groupe témoin apparié par score de propension.

Méthodes : Il s’agit d’un essai clinique prospectif. Des patients qui devaient subir une lobectomie par CTVA au Centre hospitalier de l’Université de Montréal, à Montréal, Québec, Canada, ont été recrutés entre novembre 2015 et octobre 2016. Les principes ERAS ont été appliqués à tous les patients inscrits. Le paramètre principal
Over the last decade, there has been a trend toward implementation of protocols to enhance patient recovery and decrease length of stay following surgery.1–3 Enhanced recovery protocols are commonly referred to as fast-track or enhanced recovery after surgery (ERAS) protocols. The rationale behind these protocols is that by combining multimodal therapies that reduce surgical stress and involving the patient and the treating team in this process, there is the potential to improve surgical outcomes.

Enhanced recovery after surgery pathways involve a systemic approach to the management of surgical patients, where all actions in the postoperative period are standardized and reproducible.4 Over the last few years, an increasing number of surgeons and surgical groups in various disciplines have implemented ERAS pathways. In multiple studies, authors have shown that ERAS pathways are safe and effective methods for the management of patients after pulmonary lobectomy. However, most of these studies have had methodologic limitations (observational design, lack of reproducibility, lack of a control group, and heterogeneous populations).1–3,5–8

In an era in which medical costs are on the rise, hospital beds are limited and length of stay is an important metric for hospital reimbursement, ERAS pathways have the potential to increase throughput, improve efficiency, decrease costs and improve surgical productivity.7,8 However, it is of central importance to accurately determine the impact of these pathways on the surgical recovery of patients, assess their safety and evaluate their long-term impact on the patients’ quality of life.

The objectives of this study were to implement a standardized ERAS pathway for patients undergoing a video-assisted thoracoscopic surgery (VATS) lobectomy, assess the safety and efficiency of this protocol by measuring associated postoperative outcomes, and compare the outcomes for these patients with those of propensity-matched controls.

Methods

Study design

The study consists of a prospective clinical trial (clinicaltrials.gov NCT02584322) with propensity-matched historical controls. The trial was conducted at a single regionalized high-volume university centre between November 2015 and October 2016. The study was approved by the research ethics board of the Centre de recherche du Centre hospitalier de l’Université de Montréal (CE 14.386).

Study population

The study was conducted at the Centre hospitalier de l’Université de Montréal, Notre-Dame Hospital, in Montréal, Quebec, Canada. All patients undergoing elective VATS lobectomy by any of 5 board-certified general thoracic surgeons were approached preoperatively to participate in the study. All patients eligible for the study met the study investigators at the preoperative clinic or at the hospital the night before their surgery. Those who agreed...
to participate were asked to provide consent before their surgical procedure was booked. Patients enrolled in the study underwent the exact operation they would have undergone if they had not participated in the study; the only difference was that their postoperative management followed the ERAS pathway developed for the study (Table 1). Exclusion criteria were as follows: inability to read and speak English or French, age younger than 18 years, inability to consent, and VATS lobectomy converted to open lobectomy. Data for the study patients were then compared with data for a group of propensity-matched controls who underwent successive VATS lobectomy by the same pool of surgeons in the year before the implementation of the ERAS research project. There were no secular or local trend changes in patient care between the time the control group underwent surgery and the time the ERAS group underwent surgery.

Outcomes

The primary outcome was the number and severity of complications measured by the Comprehensive Complication Index.9 Thirty-day postoperative complications were prospectively assessed from patient medical records, using the definitions developed by the American College of Surgeons National Surgical Quality Improvement Program.10 The Comprehensive Complication Index was developed by Clavien and colleagues; this tool takes into account both the number and severity of all complications and generates a score ranging from 0 to 100. The Comprehensive Complication Index is a validated measure to grade postoperative complications, and it is considered to be a more sensitive measure than traditional grading systems. The Comprehensive Complication Index has the unique property of summarizing the complete spectrum of complications the patient encounters rather than taking into account only the most severe complication, as with the Clavien–Dindo classification.11,12 The following examples illustrate this scoring system. A patient without complications is assigned a score of 0. A grade I complication (wound infection opened at bedside) receives the minimal score of 8.7, a grade II complication (pneumonia) is assigned a score of 20.9, a grade IIIa complication (atelectasis requiring a bronchoscopy) is assigned a score of 26.2 and a grade IVa complication (respiratory failure requiring intubation) is assigned a score of 42.4. A grade V complication (mortality) is assigned the maximum score of 100. When multiple complications occur, complications of lesser degree lose weight when combined with complications of higher degree. For example, a patient with both a grade I and a grade II complication is assigned a score of 22.6 and a patient with 2 grade II and 2 grade IIIa complications is assigned a score of 47.4. A 5-point difference in score is deemed to be clinically significant.12,13 Secondary outcomes for this study were length of stay, measured from the time of surgery to the time of patient discharge, and rate of 30-day readmission after discharge.

Study parameters

The following patient characteristics were recorded preoperatively: age, sex, comorbidities (used to calculate the Charlson Comorbidity Index score), height and weight (used to calculate the body mass index [BMI]), number of pack-years smoking history, diffusing capacity of the lungs for carbon monoxide (DLCO), forced expiratory volume in the first second (FEV1), type of procedure the patient underwent, and if the patient received neoadjuvant chemotherapy or radiotherapy or both.

Postoperatively, the following process outcomes were prospectively recorded: time to removal of epidural if present, time to removal of arterial line, time to nutrition, time to mobilization in chair, time to ambulation, time to removal of chest tube, presence of an air leak, and the volume of fluid present in the Pleur-evac postoperatively per 24 hours. We also recorded any visit to the emergency department up to 60 days postoperatively and any hospital readmission after discharge up to 60 days. The outcomes were manually retrieved from patient charts, which were initially transcribed by nurses, doctors, nutritionists and physiotherapists taking care of the patients clinically.

Additionally, we prospectively recorded scores on the EuroQuol 5-dimension (EQ-5D-5L) questionnaire in an attempt to evaluate surgical recovery. EQ-5D-5L is a validated measure of health-related quality of life. It is composed of 5 descriptive items graded on 3 levels that evaluate both physical and mental dimensions of a person’s health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and of a scale grading general health ranging from 0 to 100.14,15 Participants completed the EQ-5D-5L preoperatively and at both 1 month and 4 months postoperatively.

ERAS protocol

We developed an ERAS pathway that combined postoperative medical orders including nursing care, investigations and tests, and other perioperative orders, with the goal of diminishing the physiologic stress of the operation and enhancing recovery from it. We developed this ERAS pathway after reviewing the literature on the enhanced or fast-track recovery of patients undergoing thoracic surgery.7,8,16 The pathway was distributed to all thoracic surgeons, the thoracic anesthesiologists, the nurses in charge of the thoracic surgery inpatient unit and the chief pharmacist of the hospital. Comments and suggestions from all of these groups were incorporated into the final pathway before study commencement. Table 1 itemizes the main orders that are part of the ERAS pathway. This pathway
was standardized for all patients and could be discontinued at any time when clinical judgment deemed this necessary (e.g., when a patient had a severe complication) or at the surgeon’s discretion.

**Statistical analysis**

The number of patients to be enrolled in the study was calculated according to the primary outcome, which was the number and severity of postoperative complications measured with the Comprehensive Complication Index. To obtain a clinically significant difference (a 5-point difference in the Comprehensive Complication Index score), assuming a standard deviation of 12.5, a power of 90% and significance level of 0.05, the study needed to have 182 patients. If approximately 10% of patients dropped out of the study, we estimated that we needed to enrol 200 patients. To estimate the difference in mean Comprehensive Complication Index score between the ERAS group and the control group, we used a doubly robust (DR) procedure with inverse probability of treatment weighting using the propensity score (PS). Values are reported as means with standard deviations (SDs) or as medians with interquartile ranges (IQRs).

**Propensity score**

Confounders used to develop the PS included age, sex, BMI, FEV₁, DLCO, type of procedure, Charlson Comorbidity Index score and length of operation (from skin incision to skin closure). Doubly robust estimation involves the specification of both a PS model and an outcome model, and it will provide an unbiased treatment effect if either of these regression models are correctly specified. We used generalized boosted regression of surgery type on confounders to estimate the PS for each patient. We then used a Tweedie compound Poisson regression of Comprehensive Complication Index score on surgery type and confounders, with observation weights of 1/PS for the ERAS group and 1/(1 – PS) for the control group. To estimate the difference in our secondary outcome, length of stay in days, we again used a DR procedure (with the same PS model and confounders as the primary outcome) to estimate the difference in median length of stay between the ERAS and control groups. We used median quantile regression of length of stay on confounders, with observation weights of 1/PS for the enhanced recovery group and 1/(1 – PS) for the control group. All analyses were performed using R version 3.4.1.

**RESULTS**

A total of 151 potential participants were identified and assessed for eligibility to participate in the prospective part of the study, and consent was obtained from them. Fifty-three of these patients were excluded following enrollment. Thirty-five patients were excluded because their procedure was converted to thoracotomy, and 10 were excluded because they underwent a procedure that was different from the one initially planned (segmentectomy, bilobectomy or pneumonectomy). Eight patients were excluded for other reasons. The remaining 98 patients

<table>
<thead>
<tr>
<th>Table 1. Perioperative and postoperative orders for enhanced recovery after surgery pathway</th>
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<td><strong>Type of order</strong></td>
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<td>Pain control</td>
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<td>Interventions</td>
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<td>Nursing care</td>
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<td>Investigations and tests</td>
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PCA = patient-controlled anesthesia.
were enrolled in the study. Among those who were not excluded for intraoperative reasons, the participation rate was 100% (98/98). Patients in the ERAS group were compared with 98 propensity-matched controls who underwent successive VATS lobectomy by the same pool of surgeons in the year before the implementation of the ERAS research project. There were 144 patients in the control group from which the propensity-matched cohort was pulled.

**Baseline characteristics**

There were 98 patients in each group: 36 men and 62 women in the ERAS group and 29 men and 69 women in the control group. There were a total of 196 patients in the study. In the ERAS group, the mean age was 65.2 ± 9.3 years, the mean BMI was 26.9 ± 5.9 kg/m^2^ and the median Charlson Comorbidity Index score was 2 (IQR 2–3). In the control group, the mean age was 66.2 ± 9.4 years, the mean BMI was 27.5 ± 5.6 kg/m^2^ and the median Charlson Comorbidity Index score was 3 (IQR 2–3). Mean FEV₁ was 92.9% ± 18.6% and 86.8% ± 22% in the ERAS and control groups, respectively, and mean DLCO was 84.4% ± 23.3% and 83.1% ± 20.9% in the ERAS and control groups, respectively. Mean FEV₁ was 92.9% ± 18.6% and 86.8% ± 22% in the ERAS and control groups, respectively, and mean DLCO was 84.4% ± 23.3% and 83.1% ± 20.9% in the ERAS and control groups, respectively. In the ERAS group, 39 patients underwent a right upper lobectomy, 10 patients a right middle lobectomy, 10 patients a right lower lobectomy, 22 patients a left upper lobectomy and 17 patients a left lower lobectomy. In the control group, 39 patients underwent a right upper lobectomy, 3 patients a right middle lobectomy, 15 patients a right lower lobectomy, 28 patients a left upper lobectomy and 12 patients a left lower lobectomy (Table 2).

**Impact of ERAS protocol on postoperative management of patients**

In the ERAS group, time to removal of the epidural was 62.6 ± 37.2 hours, time to removal of patient-controlled analgesia was 28.9 ± 22.6 hours, time to removal of the arterial line was 2.2 ± 3.5 hours, time to nutrition was 14 ± 7.4 hours, time to mobilization to chair was 13.8 ± 7.8 hours, time to ambulation was 25.1 ± 10.9 hours and time to removal of chest tube was 65.9 ± 42.5 hours. In the control group, time to removal of the epidural was 74.8 ± 33.3 hours, time to removal of patient-controlled analgesia was 54.5 ± 22.3 hours, time to removal of the arterial line was 20.2 ± 10 hours, time to nutrition was 20.8 ± 7.8 hours, time to mobilization to chair was 27.3 ± 25.3 hours, time to ambulation was 48.2 ± 20 hours and time to removal of chest tube was 129.3 ± 114.6 hours. These results indicate that use of the ERAS protocol significantly improved all of these outcomes, except for the time to removal of the epidural (p < 0.001) (Table 3).

**Impact of ERAS protocol on postoperative complications and length of stay**

A total of 23 patients (23.4%) in the ERAS group and 28 patients (28.6%) in the control group experienced 1 or more postoperative complications. The mean Comprehensive Complication Index score was 7.4 ± 16.8 in the ERAS group compared with 8.0 ± 14.3 in the control group (p = 0.79). The median postoperative length of stay was 3 days (IQR 2–5 d) in the ERAS group and 5 days (IQR 4–6 d) in the control group. In the presence of all other variables included in the propensity model, there was not enough

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<th>Table 2. Patient characteristics</th>
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<td>Characteristic</td>
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<td>Age, yr</td>
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<td>Male sex, no. (%) of patients</td>
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<td>Charlson Comorbidity Index score, median (IQR)</td>
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<td>BMI, kg/m²</td>
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<td>Type of surgery, no. of patients</td>
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<td>FEV₁, %</td>
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<td>DLCO, %</td>
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<td>Length of operation, h</td>
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BMI = body mass index; DLCO = diffusing capacity of the lungs for carbon monoxide; ERAS = enhanced recovery after surgery; FEV₁ = forced expiratory volume in the first second; IQR = interquartile range; SD = standard deviation.

*Unless indicated otherwise.
Evidence from the model to suggest that patients in the ERAS group experienced significantly fewer or more complications than patients in the control group (p = 0.79). In the presence of all other variables included in the propensity model, there was enough evidence to suggest that being part of the ERAS group was associated with a decrease of 0.77 days in median length of stay (p < 0.001).

Adherence to ERAS protocol and impact of ERAS protocol on readmission

The percentage of patients who fully adhered to the ERAS protocol in our study was 64.3% (63/98). Five patients were readmitted in the ERAS group and 4 patients were readmitted in the control group. The reasons for readmission were subcutaneous emphysema (3 patients), pneumothorax (1 patient) and empyema (1 patient) in the ERAS group, and pleural effusion (1 patient), empyema (1 patient), delirium (1 patient) and pancreatitis (1 patient) in the control group. Although the readmission rate appears to be comparable between the 2 groups, it is important to note that this study was not powered to evaluate this outcome.

Recovery after VATS lobectomy

The mean EQ-5D-5L score for patients in the ERAS group was 8.8 ± 1.3 preoperatively and 7.3 ± 1.9, 8.1 ± 1.6 and 8.9 ± 1.1 at 1 week, 1 month and 4 months after surgery, respectively (Fig. 1). The EQ-5D-5L health score was 77.1 ± 15.8 preoperatively and 64 ± 19.6, 73.8 ± 15.8, 76.4 ± 15.7 at 1 week, 1 month and 4 months after surgery, respectively.

Discussion

In an era when hospital costs are increasing, length of stay is critical and patient care is heavily scrutinized, enhanced recovery is becoming increasingly important in the management of patients after surgery. To date, most of the research on enhanced recovery has been carried out in the field of gastrointestinal surgery. This research has led to the development of evidence-based ERAS pathways, task forces providing guidelines for the establishment of ERAS pathways for early adopter institutions necessitating mentoring, and task forces trying to continuously improve these pathways.22-24 In the field of thoracic surgery, several studies have investigated the implementation of these pathways; however, ERAS in thoracic surgery is still in its infancy and has not been widely implemented.8,25

With the increasing numbers of surgeon performing VATS lobectomy, evidence-based ERAS protocols for this procedure need to be developed and widely adopted.26 It is therefore essential to develop robust protocols and to evaluate their safety and efficacy to enable widespread implementation in centers performing this type of surgery. This prospective trial with propensity-matched historical controls was performed to determine the safety of the implementation of an ERAS pathway that was developed in a single high-volume institution and to assess the impact of this protocol on postoperative complication rates, readmission rates and postoperative length of stay.

This study demonstrated that the use of an enhanced recovery pathway is no more dangerous for patients than usual care and that it did not increase readmission rates. It was associated with a significantly decreased length of stay. These findings have important clinical consequences for the management of patients undergoing VATS lobectomy. However, there is still a lot of work to do to enable widespread implementation of enhanced recovery pathways. Task forces need to be created to optimize protocols and provide resources for institutions interested in implementing ERAS. Given the variety of pathways reported in the literature, we believe consensus needs to be established regarding pathway components. Examples include the timing of the insertion of

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<td>Time to removal of chest tube, h</td>
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<td>Comprehensive Complication Index score</td>
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<td>Length of stay, d, median (IQR)</td>
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<td>Readmission, no. of patients</td>
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ERAS = enhanced recovery after surgery; IQR = interquartile range; PCA = patient-controlled analgesia; SD = standard deviation.

*Unless indicated otherwise.
a Heimlich valve for patients with prolonged air leak and the follow-up necessary for those patients, the need for chest x-ray postoperatively, the type of postoperative pain control used, and the timing of removal of the epidural/paravertebral catheter when the operation has been successfully performed via thoracoscopy.

Our study prospectively assessed quality of life after VATS lobectomy. The results showed that recovery after lobectomy is a long process, which can take up to 4 months for certain patients. These results are consistent with previous research on surgical recovery after major abdominal recovery. Surgical recovery is a process that starts at the hospital and continues at home. This process coincides with the goals of ERAS protocols, which are to enable the patient to go home as soon as their medical condition permits and to continue to recover in an environment they know well, free of the risk of nosocomial infection and potential medical mistakes.

Brunelli and colleagues assessed the impact of the implementation of an ERAS protocol on patients undergoing VATS lobectomy. They were not able to find any differences in the incidence of complications, length of stay and readmission rates between the pre- and postimplementation groups. The study had several limitations: it had a retrospective design, there was a short washout period, most elements of the ERAS protocol were being used in the preimplementation period and the degree of protocol adherence was unclear. However, it highlights 2 important points: the commitment needed to implement an ERAS protocol, and the potential lower impact of an ERAS protocol in a centre that is already using ERAS point-of-care parameters.

Limitations

Our study has several limitations. First, it was observed that for several patients in the ERAS group, surgeons did not fully adhere to the ERAS protocols because they felt that certain elements of the protocol at particular time points were inappropriate for certain patients. This highlights 2 important points linked to the implementation of ERAS protocols in any institution. First, it is important to always allow surgical judgment to supersede the protocol to prevent complications in certain patients. The protocol is designed with most patients in mind; however, it cannot be applied blindly to all patients. On the other hand, there may be experienced surgeons who have been managing their patients in a specific manner for many years who do not want to follow ERAS protocols, despite the fact that they represent the modern-day standard of care. This is well illustrated in our study with the epidural component of our ERAS protocol. Many surgeons and anesthesiologists decided to insert epidural catheters in their patient because of the risk of conversion to thoracotomy, and several patients kept their epidural catheter past the first postoperative day, even though the protocol specified removal of the epidural catheter as per surgeon’s choice.

We can hypothesize that this limitation probably only underestimated the impact of the protocol and that reduction of epidural use can enhance the positive impact of our ERAS pathways. However, this limitation also highlights the challenges of implementing an ERAS protocol in a large institution with multiple surgeons and anesthesiologists. The percentage of patients who fully adhered to the ERAS protocol in our study was 64.3%; we believe that in future studies, a washout period of 3 months could be used to maximize protocol compliance. Second, ERAS protocols should start in the preoperative clinic, with the patient being coached regarding the protocol and being involved in the process. However, we did not have the human resources required to teach patients about the ERAS protocol in the preoperative clinic. We overcame this limitation by explaining the process the night before the operation and by hanging large posters in the thoracic surgery ward explaining ERAS recovery. All patients also received pamphlets explaining the ERAS protocol and the target goals for each day during the ERAS protocol. Another limitation of the study is the learning curve associated with the use of protocols. When an ERAS protocol is used with new trainees (residents, fellows) who are not familiar with the ERAS concept, they sometimes lack surgical judgment and may try to send the patient home too early. This can sometimes lead to a nonresolved air leak being overlooked in the context of an ERAS protocol. We believe this led to 4 of our 5 readmissions in the ERAS group, with 3 patients returning to hospital with subcutaneous emphysema and 1 with pneumothorax. This complication may be decreased with digital pleural drainage systems that precisely monitor air leak. The teaching of trainees is therefore also very important before an ERAS protocol is implemented. An additional limitation of the study is the fact that we excluded patients whose procedure was converted to open
surgery; this was intentional. The goal of this study was to measure the impact of the implementation of an ERAS protocol on patients undergoing VATS lobectomy and to compare their results exclusively with the results of propensity-matched controls who underwent VATS lobectomy. Finally, the choice of the set of orders that constitute our ERAS protocol may seem arbitrary (e.g., complete blood count and chemistry on the first postoperative day) and may be considered by some to be not sufficiently fast-tracked. However, this protocol was agreed upon after a thorough review of the literature and after it was distributed to and validated by all of the thoracic surgeons and thoracic anesthesiologists involved in the project. This limitation highlights the need for task forces to provide consensus guidelines for the establishment of ERAS pathways.

**CONCLUSION**

It is feasible to implement an ERAS pathway following VATS lobectomy. Although such pathways are still early in their development and implementation is still incomplete, we found that implementation of enhanced recovery after VATS lobectomy is associated with a decreased length of stay, with no observable increase in complication or readmission rates.

**Affiliations:** From the Division of Thoracic Surgery, Université de Montréal, Montréal, Que. (Tahiri, Goudie, Jouquan, Thiffault, Martin, Ferraro, Liberman); and the CHUM Endoscopic Tracheobronchial and Oesophageal Centre (CETOC), Montréal, Que. (Tahiri, Goudie, Jouquan, Thiffault, Martin, Ferraro, Liberman).

**Competing interests:** None declared.

**Contributors:** M. Tahiri, E. Goudie, P. Ferraro and M. Liberman designed the study. M. Tahiri, E. Goudie, A. Jouquan, J. Martin, P. Ferraro and M. Liberman acquired the data, which M. Tahiri, E. Goudie, P. Ferraro and M. Liberman analyzed. M. Tahiri, E. Goudie and M. Liberman wrote the manuscript, which all authors critically reviewed. All authors gave final approval of the article to be published.

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