Review Article

Enhanced recovery pathways in thoracic surgery from Italian VATS Group: preoperative optimisation

Antonio D'Andrilli[1], Domenico Massullo[2], Erino A. Rendina[1]

[1]Department of Thoracic Surgery, [2]Department of Anaesthesiologyy, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy

Contributions: (I) Conception and design: A D'Andrilli; (II) Administrative support: A D'Andrilli, EA Rendina; (III) Provision of study materials or patients: A D'Andrilli, D Massullo; (IV) Collection and assembly of data: A D'Andrilli; (V) Data analysis and interpretation: A D'Andrilli; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Antonio D'Andrilli, MD. Department of Thoracic Surgery, Sant'Andrea Hospital, Sapienza University of Rome, Via di Grottarossa 1035, 00189 Rome, Italy. Email: adandrilli@hotmail.com.

Abstract: Preoperative patient optimisation is a key point of enhanced recovery after thoracic surgery pathways. This could be particularly advantageous when considering video-assisted thoracic surgery (VATS) lobectomy, because reduced trauma related to minimally invasive techniques is one of the main factors favouring improved postoperative outcome. Main specific interventions for clinical optimisation before major lung resection include assessment and treatment of comorbidities, minimizing preoperative hospitalization, optimisation of pharmacological prophylaxis (antibiotic and thromboembolic) and minimizing preoperative fasting. Literature data and clinical evidences in this setting are reported and discussed.

Keywords: Video-assisted thoracic surgery (VATS); lobectomy; fast-track surgery

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Introduction

Enhanced recovery after thoracic surgery protocols, in agreement with those proposed in other surgical disciplines, have been primarily developed to prevent factors of delayed postoperative recovery, and are established to achieve faster mobilization and resumption of regular activities with no increased or even decreased complication rate (1,2). Furthermore, reduction of perioperative complication rate is considered one of the primary goals to be reached to decrease length of hospital stay and related costs.

Interest in fast-track pathways can be furtherly increased when considering video-assisted thoracic surgery (VATS) lobectomy, because reduced trauma related to minimally invasive techniques is one of the main factors favouring improved postoperative outcome (3,4).

Basic principles of these protocols promote a multidisciplinary approach since the first observation of the patient who is candidate to minimally invasive major lung resection, with the aim of optimising all the aspects of perioperative and intraoperative management on the basis of evidence-based best medical practice.

A large body of evidences has been published demonstrating that optimising clinical status of the patient before colorectal (5), breast (6), pancreatic (7), and urological (8) surgery may allow to reduce the physical and psychological stress related to the operation and to promote restoration of function. However, there is still paucity of similar reports in thoracic surgery, and specifically in lung cancer surgery, with no published data concerning enhanced recovery after surgery (ERAS) in VATS lobectomy.

A key point of ERAS protocols is that all patients who are going to receive elective surgery should undergo preoperative general assessment with the aim of establishing if they are fit for the planned operation. Especially in the case of patients with poor performance status, accurate preoperative evaluation should start as soon as possible after the initial diagnosis, and should include detailed patient history and clinical assessment, blood exams including basic metabolic panel and complete blood count, and

measurements of pulmonary and cardiac function. It is very important to identify patient risk factors adequately in advance before surgery, to allow appropriate arrangements and interventions for possible preoperative optimisation.

Main specific interventions for clinical optimisation in the preoperative phase include:

- Assessment and treatment of comorbidities with special interest for those that can be modified within the interval of time between the first patient observation and the operation;
- Minimizing preoperative hospitalization;
- Optimisation of pharmacological prophylaxis (antibiotic and thromboembolic);
- Minimizing preoperative (as well as post-operative) fasting.

There are some other fundamental parts of preoperative optimisation such as physiotherapy and information of patients and their families, but these are not among the topics of this chapter and will be discussed elsewhere.

Patient optimisation for comorbidities and risk factors

Assessment of comorbidities and risk factors is a crucial point of patient evaluation in the preoperative phase. There is clear evidence in the literature that the presence of significant comorbidities increases the risk of post-operative complications, and that preoperative treatment of comorbidities and patient optimisation may contribute to significantly reduce complications after surgery. Unfortunately, there are many risk factors which cannot be modified with a specific treatment in a limited period of time, and therefore clinical intervention should be principally directed to those comorbidities that could be optimised during the interval between initial diagnosis and surgical treatment (generally few weeks).

Main pathologic conditions increasing the perioperative risk which can be treated and optimised whilst awaiting surgery include: anaemia, malnutrition, chronic obstructive pulmonary disease (COPD) and active smoking. These conditions will be discussed in the present chapter. Other frequent comorbidities such as diabetes and hypertension may only require optimisation of therapy for patients who have not adequate disease control, but the status of disease can hardly be modified before surgery. Additional conditions that significantly increase the surgical risk, such as obesity and alcohol abuse, have to be identified and considered when planning the operation, although they cannot be effectively treated in a short period of time before surgery.

Anaemia is defined as the deficiency of red cells in blood with hemoglobin concentration <13 g/dL in males or <12 g/dL in females. It is a common incidental finding in patients with cancer and therefore also in patients with lung cancer. There are evidences that the presence of anaemia increases perioperative morbidity and mortality of patients undergoing surgery (9). Therefore, it should be identified, investigated and treated before elective surgery. Blood transfusion is the most common method to improve hemoglobin levels in anaemic surgical patients. However, it can be associated with a higher risk of complications such as acute transfusion reactions, immunosuppression, post-operative infections that may be responsible of prolonged hospital stay (10). For this reason, in the preoperative setting, transfusion is usually reserved only to patients with severe anaemia (hemoglobin concentration <8 g/dL). Alternative strategies to treat minor degrees of anaemia include iron supplementation and erythropoietin, whose administration is associated with significantly lower complication rate and may contribute to reduce the need for transfusion. Although the beneficial effect of anaemia treatment in the perioperative period are well known, in the literature the utility of the latter therapeutic methods has been only assessed in the context of lung cancer patients undergoing adjuvant chemo- or radiotherapy (11), and there is still paucity of data in the surgical setting. In current clinical practice and in the context of ERAS pathways, preoperative treatment of anemia with iron supplementation or erythropoietin is generally recommended for all patients with haemoglobin level <10 g/dL.

Malnutrition is another relatively frequent condition in patients with cancer. The rate of patients with operable lung cancer showing a severe malnutritional status preoperatively has been reported up to 28% in some studies (12). This condition is associated with increased risk of impaired wound healing, immune dysfunction, muscle wasting with respiratory fatigue in the postoperative period. These problems result in delayed patient recovery and prolonged hospitalization. There is therefore a strong recommendation for screening malnutrition before surgery. Current guidelines also recommend (grade A evidence) that patients found with severe preoperative nutritional risk should receive nutritional support for at least 2 weeks before major surgery (13).

Definition of severe nutritional risk has been codified as the presence of at least 3 of the following conditions:

weight loss >10–15% within last 6 months, body mass index (BMI) <18.5 kg/m^2, Subjective Global Assessment Grade C, and serum albumin level <30 g/L with no coexisting hepatic or renal dysfunction.

In a French study enrolling almost 20,000 patients who underwent major lung resection in main national centres, the presence of a preoperative malnutritional status has shown a statistically significant impact on postoperative morbidity and mortality. In particular, there was a significant increase in operative death rate, surgical complication rate, respiratory complication rate and infectious complication rate in patients with preoperative BMI< 18.5 kg/m^2 (14).

To date there are still no definitive recommendations regarding the type of nutritional support to use before lung cancer surgery. Moreover, there is lack of data examining the impact of preoperative correction of poor nutritional status in lung cancer patients. Differently, some small prospective studies are available assessing the benefits of preoperative nutritional support in patients undergoing major resection for lung cancer with normal nutritional status.

A recent prospective randomized study has compared the postoperative outcome of 31 patients undergoing resection for non-small cell lung cancer (NSCLC) who received preoperative protein rich nutrition support (arginine, omega-3-fatty acids and nucleotides) for 10 days with the postoperative outcome of 27 patients receiving only normal diet. Thirty-five percent of patient in the experimental group and 40% in the control group were operated with VATS technique. This study showed that preoperative nutrition was beneficial in decreasing the complication rate (19% *vs.* 44%) and mean chest tube removal time (4 *vs.* 6 days) (15).

Another small prospective randomized trial has investigated the effect of micronutrient supplementation in postoperative outcome of patients with normal BMI who underwent lung cancer surgery (16). In this study a combination of alpha-ketoglutaric acid and 5-hydroxymethylfurfural not only improved exercise capacity and reduced oxidative stress, but also resulted in a significant reduction in intensive care unit stay and postoperative hospitalization.

COPD is a frequent finding in patients undergoing lung cancer surgery, and is related with increased risk of postoperative pulmonary complications. There are several published studies showing that optimisation of the pharmacological therapy before surgery has a beneficial impact improving respiratory function and reducing the risk of pulmonary complications. In a prospective study including patients with untreated functional airway obstruction, those receiving a long acting bronchodilator treatment before surgery showed a significant improvement in preoperative global pulmonary function. Postoperative outcome was significantly better in major responders than in minor responders (17).

In another prospective randomized study analyzing patients with untreated COPD, the addition of inhaled steroid to long acting bronchodilator was related with improved preoperative FEV1 and decreased postoperative pulmonary complication rate (18) compared to long acting bronchodilator alone. There is also evidence that pharmacological optimisation associated with respiratory physiotherapy in the preoperative setting may result in significant functional improvement allowing the operation in patients previously considered unfit for surgical resection (19). Based on current available data, optimisation of pharmacological therapy associated with respiratory physiotherapy should be recommended in functionally compromised patients with the aim of improving respiratory function and reducing perioperative morbidity.

Active smoking is generally reported as a significant risk factor for increased postoperative complication rate and mortality rate after major lung surgery (20). There is also clear evidence in the literature that smoking cessation may reduce perioperative morbidity and mortality (20,21). In a study from the Society of Thoracic Surgeons Database hospital mortality was 1.5% in patients who had smoked compared to 0.4% in patients who had not. Prevalence of major pulmonary complications was 6.2 % in current smokers and 2.5% in non-current smokers (21). However, there are some published studies suggesting that smoking cessation immediately before NSCLC resection does not significantly impact postoperative pulmonary complication rate and therefore should not be the reason to delay surgical resection (22). Moreover, in other studies there is no evidence of a paradoxical increase in pulmonary complications among patients who quit smoking within 2 months of undergoing surgery (23). In general, benefits of smoking cessation are as higher as longer is the time of cessation before surgery. Musallam and colleagues report that smoking cessation at least 1 year before major surgery abolishes the increased risk of postoperative mortality and decreases the risk of arterial and respiratory events evident in current smokers (20).

Current guidelines for lung cancer patients' management recommend that smoking cessation should be always encouraged as soon as possible before surgery; however, the operation should not be postponed to allow this (23).

Nicotine replacement and other therapies to help stop smoking are also recommended (24).

Preoperative hospitalization

There is evidence that prolonged hospitalization produces a negative psychologic impact on patient with potential effect on immune defence. Effective preoperative assessment, with identification and optimisation of main risk factors before hospitalization, has been proved able to reduce surgery delay or cancellation rate and increase patient satisfaction making prolonged preoperative hospitalization unnecessary. As a consequence, hospitalization before surgery can be significantly shortened, and same-day admission or admission the night before surgery for patients undergoing operation early in the morning can become the rule. This aspect, together with previous adequate detailed explanation of the intended perioperative pathway, also contributes to reduce patient anxiety with a favourable impact on postoperative outcome, thus decreasing the perioperative costs (2).

Antibiotic prophylaxis

Appropriate prophylactic antibiotic therapy has been shown to reduce infectious complication rate after thoracic surgery. No official guidelines exist for perioperative antibiotic use in noncardiac thoracic surgery. Despite some conflicting data and few randomized clinical trials, strong evidence exists supporting the use of perioperative antibiotic prophylaxis in pulmonary resection (25). Currently, no special indication has been provided in this setting for ERAS pathway and for VATS lobectomy, therefore general rules used in lung surgery can be used.

Since preoperative airway colonization with pathogens represents a significant risk factor for the occurrence of lung infections after thoracic surgery, special care must be taken when managing patients with COPD or abundant bronchial secretions. These patients may have received previous repeated antibiotic treatments with possible changes in usual pattern of flora and potential development of antibiotic resistance. The choice of prophylactic antibiotics is based on the most common pathogens likely to result in infections of the surgical site. In pulmonary surgery bacteria from normal skin and respiratory flora are the most common cause of infection. These include *Staphylococcus Aureus*, coagulase-negative staphylococci, *Streptococcus Pneumoniae* and gram-negative bacilli, with *S. Aureus* being the most frequently identified pathogen (26). Main systematic reviews and randomized controlled trials show that first-generation cephalosporins, such as cefazolin, which provide adequate coverage for the most common pulmonary surgical site infections, are an appropriate choice for prophylactic antibiotic therapy. The appropriate dosage for cefazolin is 1–2 g I.V. prior to incision (27). Second-generation cephalosporins can be used as second choice. If the patient has history of methicillin-resistant *S. Aureus* or a penicillin allergy, then vancomycin 1 g I.V. can be used in place of cefazolin. Other alternative antibiotic to be used in case of allergy are macrolides (clindamycin).

According to the World Health Organization (WHO) Safer Surgery checklist (28) the preoperative administration of antibiotic should be performed 60 minutes or less before surgical incision. Ideal time is 30 minutes or less before the operation.

Thromboembolic prophylaxis

Based on observational studies, most patients undergoing lung cancer surgery should be considered at least at moderate risk for postoperative venous thromboembolism (VTE). In one study of 693 thoracotomies for lung cancer, symptomatic VTE was observed in 1.7% of patients despite routine use of pharmacological prophylaxis (29). In another analysis of 706 thoracic surgery patients, pulmonary embolism occurred in 7% of patients who did not receive prophylaxis, but there were no episodes of PE in patients receiving mechanical prophylaxis (29). VATS lobectomy is classified as a non-high bleeding risk operation. Therefore, since there are still no approved guidelines for VTE specifically in ERAS protocols, general guidelines for lung resection in patients with non-high bleeding risk should be used. American College of Chest Physicians (ACCP) guidelines for VTE prophylaxis recommend the following management:

- For patients with low risk for VTE: no prophylaxis or mechanical prophylaxis only (anti-embolism stockings, intermittent pneumatic compression devices or foot impulse devices);
- For patients with moderate VTE risk (Caprini score 3–4): pharmacological prophylaxis with low molecular weight heparin (LMWH) for 7–10 days or until discharge. Association of mechanical prophylaxis is optional;
- For patients with high VTE risk (Caprini score ≥5): pharmacological prophylaxis with LMWH associated

with mechanical prophylaxis (anti-embolic stockings or intermittent pneumatic compression devices) for 7–10 days or until discharge.

Preoperative fasting

Prolonged preoperative fasting may be responsible of metabolic and psychological stress. Fasting from the midnight before lung surgery has been a standardized rule in the past, and is still a persistent practice in many thoracic surgery units worldwide in order to reduce the risk of bronchial inhalation during anaesthesia and in the immediate postoperative period.

Currently there is a large body of literature data showing that shorter preoperative fasting is not related with increased perioperative complication rate. A systematic review appeared in 2003 led to conclusion that preoperative fasting period for clear fluids can be safely reduced to 2 hours without increased complication rate (30). Recent guidelines from the European Society of Anaesthesiology (31), based on a high level of clinical evidence, recommend that all patients undergoing lung cancer surgery without specific risk factors for inhalation should be encouraged to drink clear fluids (including water, pulp-free fruit juice, tea and coffee without milk) up to 2 hours before elective surgery. According to the large majority of the members of the guidelines, tea and coffee should be still considered clear fluid with milk added up to about one third of the total volume. Solid food should not be prohibited up to 6 hours before elective surgery. In general, a light meal with toasted bread and liquids can be allowed up to 6 hours preoperatively, while a regular meal including fried or fatty food can be allowed up to 8 hours before surgery (31). There is now a large body of data showing that abstaining from fluids for a prolonged period prior to surgery is detrimental for patients; it is therefore important to encourage patients to keep drinking up until 2 hours before surgery to reduce their discomfort and improve their well-being (32,33). A previous study has shown that gastric volume was not increased after a light breakfast of tea and buttered toast consumed 2–4 hours before elective surgery (34). There is also a high level of evidence (coming from some prospective randomized trials) showing that drinking carbohydrate-rich fluids before elective surgery improves subjective well-being, reduces thirst and hunger and reduces postoperative insulin resistance (35,36). The evidence for safety is derived from studies of products (predominantly maltodextrins) specifically developed for perioperative use. Therefore, preoperative oral intake of carbohydrates has to be considered beneficial and safe up to 2 hours before elective surgery.

Conclusions

There is evidence that preoperative optimisation of the patient before major surgery including lung cancer surgery may allow to significantly reduce postoperative complication rate. This should therefore consider a fundamental part of enhanced recovery after thoracic surgery pathways. In the era of minimally invasive surgery the application of such principles could provide increased advantage in the perioperative outcome of patients undergoing VATS lobectomy.

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