Review Article

Interventions to avoid pulmonary complications after lung cancer resection

Patrick James Villeneuve

Division of Thoracic Surgery, Department of Surgery, The Ottawa Hospital, Ottawa, Ontario, Canada

Correspondence to: Patrick James Villeneuve, MDCM, PhD, FRCSC. Division of Thoracic Surgery, Department of Surgery, The Ottawa Hospital, 501 Smyth Road, Room 6362, Ottawa, Ontario K1H 8L6, Canada. Email: pvilleneuve@toh.ca.

Abstract: Surgical resection of lung cancer is the preferred treatment for early-stage disease in medically fit patients. The rates of postoperative pulmonary complications (PPCs) such as pneumonia, empyema and atelectasis are as high as 10% in contemporary series. A review of the literature was performed to identify the best evidence supporting interventions to identify, prevent and treat PPCs. The use of patient risk scores, appropriate choice of antibiotic prophylaxis, intraoperative ventilatory strategies, chest physiotherapy, sputum management and non-invasive ventilatory support were specifically discussed, as was the relevant supporting data. Recommendations to guide best practice and inform future research questions are outlined.

Keywords: Postoperative complications; lung cancer; pulmonary resection; evidence-based medicine

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Introduction

Lung cancer is the most common cause of cancer related death worldwide, with an estimated 28,600 new cases and 21,100 deaths in Canada in 2017. Despite a decrease in lung cancer mortality more recently, lung cancer continues to have the highest mortality rate, and 26.2% of cancer deaths will be related to lung cancer (1). Surgical resection in medically fit patients provides the highest likelihood of cure in early-stage disease, and is however associated with a risk of postoperative complications. In a recent 4-year retrospective study (2) of 670 patients undergoing lung resection, pneumonia and atelectasis were found to be the most common postoperative pulmonary complication (PPC), with a 13% incidence (n=88). They identified patients with PPC based on increased white cell count, increased oxygen requirement, purulent sputum production or findings on chest radiograph. Significantly, the development of PPC was associated with increased length of stay (LOS), longer stay in intensive care, as well as increased 30- and 90-day mortality. A more recent determination of the rate of PPC was obtained as part of the ACOSOG Z0030 multi-centre study (3); in this series the rates of pneumonia were found to be 2.5%, empyema 1.1% and atelectasis 6.4% which represented a combined PPC rate of 10%. A retrospective analysis of prospective collected data at our institution has demonstrated (4,5) that the development of any complication is associated with both increased LOS and decreased patient satisfaction. It is therefore imperative to continue evaluating and refining postoperative care, in order to provide best care and ensure optimal outcomes.

The recommendations outlined herein are meant to represent a useful and practical review of evidence-based practices that could inform practice changes or further trials in the area of perioperative care for lung cancer resections.

This is a narrative review of the literature aimed at synthesizing the information contained within selected randomized trials, meta-analyses and practice guidelines. It is possible that relevant articles have been omitted. We have also chosen to solely concentrate on the review of studies of patients undergoing lung cancer resection, although some studies with mixed cardiothoracic patient populations were included. The search strategies were applied to MEDLINE from the period 1946 to 2018 in order to identify the relevant literature for inclusion and analysis. Only papers within the last 20 years were considered for review and inclusion. Refer to Supplementary file for the specific search terminology used. Based on this review of the literature, a series of randomized trials, systematic reviews and meta-analyses have been selected for further discussion herein.

There are several important elements of preoperative, perioperative and postoperative care that can be optimized to achieve overall reduction in complications. These include, but are certainly not limited to: smoking cessation, preoperative physical optimization, effective analgesic strategies, arrhythmia control, prevention of parenchymal airleaks, improved chest drain management, as well as the incorporation of ERAS pathways into routine post-resection care.

Attention will be focused in this article to interventions for reducing the development of as well as the treatment of PPCs—the reduction of sputum retention, lung injury and pneumonia.

Identification of patients at risk

The provision of high-quality surgical care mandates minimizing perioperative complications by identifying and mitigating factors known to contribute to poor outcomes. The specific issues of preoperative risk mitigation will be addressed in a companion article in this issue of the journal.

The relative utility of risk scoring systems in thoracic surgery has been carefully examined by Ferguson and Derkin (6). They used a historical cohort of 400 patients over the period 1980–1995 to derive a risk scoring schema (EVAD). The elements of the EVAD score were (I) percent predicted FEV1, (II) age and (III) percent predicted DLCO. The score was calculated as follows: A maximum score of 12 points is possible, with at most 4 possible points per variable. For both FEV_1 and DLCO, each decrement of 10% predicted from a baseline of 90% predicted counted for one point. Similarly, each decade of age beyond 50 years counted as one point.

The EVAD score was then compared to the Physiological and Operative Severity Score for Enumeration of Mortality and Morbidity; POSSUM (7) and the Cardiopulmonary Risk Index; CPRI (8). For this comparison the study authors used a separate validation cohort of 219 patients over the period from 1996 to 2001. The authors were able to demonstrate that the EVAD score had superior predictive scores and has been shown to accurately predict postoperative complications of any sort (mean EVAD score of 7.4). As could be anticipated by the variables imputed, this score was unable to predict complications related to infections in particular. The statistical performance of the model was limited, and as such its general applicability can be questioned.

Nevertheless, predictive risk scores are useful in identifying high-risk patients early to allow for implementation of appropriate preventative strategies to optimize recovery. The wider use of the EVAD score, or any validated risk stratification model is strongly recommended in order to avoid PPC. In practice, despite many predictive scores being available, it is this author's opinion that the variables making up the EVAD score are readily accessible to the surgeon in clinic, and is thus easy to calculate. It is therefore recommended that broad use of a risk score be used in the assessment of patients prior to lung cancer resection.

Best choices for antibiotic prophylaxis

The use of first-generation cephalosporins just prior to skin incision has been demonstrated and is agreed to be to most effective means for prophylaxis of most surgical site infections (SSIs) (9) related to skin flora. The rate of SSI in thoracic surgery is low, reported as between 0.76–2% and is lower when minimally invasive approaches are applied (5.5% *vs.* 14% after thoracotomy). Pneumonia can be considered an organ-space SSI (10) which has reported rates of 3–24% even with appropriate antibiotic prophylaxis. Current recommendations advocate the use of a single dose of cefazolin or ampicillin sulbactam, while vancomycin and clindamycin are recommended for documented beta-lactam allergies. There is minimal coverage from cephalosporins or vancomycin for the resident airway flora.

In a 6-month prospective study of lung cancer resections (11), pneumonia was found to occur in up to 25% of patients despite prophylactic antibiotic therapy; with a 10-fold higher mortality rate as compared to patients without pneumonia (19% *vs.* 2.4%). Pneumonias were diagnosed using intraoperative bronchoscopy aspirates. The most commonly isolated organisms in this study included *Haemophilus spp*. (41%), *S. pneumoniae* (25%) and *Pseudomonas spp*. (25%).

The appropriateness of skin-specific antibiotic prophylaxis can therefore be questioned given the low rates of wound SSI as compared to deep organ SSI (pneumonia) in post lung resection patients. In an attempt to address this, a prospective cohort study of 478 patients undergoing elective lung cancer resection was performed (12), comparing the second-generation cephalosporin cefamadole

(CEF; 1.5 grams IV at induction with 3 grams daily for an additional 48 h) with amoxicillin-clavulanate (AC; 2 grams q8h for three doses). A total of 168 patients were treated with CEF over the first 6 months of the study, and the subsequent 277 received AC over the remaining 12 months of the study. *Post-hoc* matching was performed to address potential confounders between the groups in the absence of randomization. The rate of pneumonia was reduced from 27% to 14% in the period where AC was used (P=0.048). Mortality, while not statistically different between the groups, was reduced from 6.5% to 2.9% when Amoxiclav was used. A reduced ICU LOS was also observed in the second study period (5.6 *vs.* 4.8 days). No difference was observed in the rates of wound infection, empyema, or sputum retention requiring bronchoscopy in the two groups. Despite the methodological shortcomings of the study design, the results reported are provocative.

No randomized control trials have been performed that specifically address the ideal choice of prophylactic antibiotics for pulmonary resection, and represents an opportunity for further investigations. The best data to date, however suggests that the selection of antibiotics with a spectrum of action effective against respiratory flora is a better choice to prevent PPC after lung surgery, rather than antimicrobials with more effect against skin flora.

Intraoperative ventilatory strategies

The importance of lung protection when establishing ventilator parameters has been understood since the first reports from the ARDSnet trials in the ICU setting (13). The use of lung protective strategies is of importance when considering the unique considerations of one-lung ventilation (OLV) during lung resection. Lung protective strategies are generally accepted as using tidal volumes of 4–6 mL/kg, modest positive end-expiratory pressures (PEEP) less than 10 cmH_2O and employing pressure-controlled ventilator modes (14).

A cohort of patients (n=100) undergoing elective lobectomy were randomized to conventional or protective ventilatory strategies when undergoing single-lung ventilation (15). Primary endpoint in this study was the development of lung injury within 72 h of surgery, defined as hypoxemia (PaO_2:FiO_2 ratio of <300 mmHg) and/or radiographic evidence of lung injury (infiltrates or atelectasis). Fifty patients were randomized to conventional OLV (FiO_2 of 1, tidal volume 10 mL/kg, no PEEP and volume-control settings) and another 50 patients to the protective OLV (FiO_2 of 0.5, tidal volume 6 mL/kg, 5 cmH_2O PEEP and pressure-control settings). The study found that pulmonary injuries were significantly reduced in the protective OLV group (4% *vs.* 22% with P<0.05). Unfortunately, no mortality or measurements of PPC rates were obtained during the study, and it is possible that this study is underpowered due to the overall rarity of ARDS.

A more recently reported study (16) sought to evaluate the effect of lung protective ventilation on the development of PPC. The study spanned 2008–2011 and was a randomized study of 346 patients undergoing lung resection (lobectomy or pneumonectomy); 172 patients were randomized to protective OLV (tidal volume 5 mL/kg and PEEP 5–8 cmH_2O) and an additional 171 patients received conventional OLV (tidal volume 10 mL/kg and no PEEP). Primary outcome was the development of PPC (authors also included pulmonary emboli, myocardial ischemia and death in the primary outcome) that occurred in the first 30 postoperative days.

The rate of major complications (primary outcome) was significantly less in the protective OLV group (13.4% *vs.* 22.2% with P=0.03), as were the secondary outcomes of atelectasis (37.2% *vs.* 49.9% with P=0.02) and hospital LOS (11 *vs.* 12 days with P=0.048). Although this study was closed prematurely due to insufficient accrual, the authors were able to demonstrate an advantage to lung protective ventilation strategies in patients undergoing lung cancer resection.

Chest physiotherapy

One of the most commonly recommended interventions to prevent PPC is postoperative chest physiotherapy. This generally involves a series of exercises to promote deep breathing, facilitate sputum clearance and enhance mobility (17). Patients undergoing lung cancer resection may have a lower rate of postoperative complications when they participate in a preoperative exercise (18) program. A reduction in both postoperative complications and LOS has been described. Chest physiotherapy represents the mainstay of postoperative care. This has been shown to significantly reduce the rate of PPC from 15.5% to 4.7% (P<0.001) after lung cancer surgery (17), which was demonstrated in a retrospective, propensity matched study of 784 patients divided into two periods of before (n=361) and after introduction of dedicated chest physiotherapy.

The efficacy of standard postoperative physiotherapy and the effect of incentive spirometry (19) was recently examined in 387 patients undergoing lung resection over a 3-year period. Patients were randomized to physiotherapy (PT) alone (n=192) or the addition of an incentive spirometer (+ IS) to standard PT (n=195). The interventions were blinded by the use of a box placed at the bedside in which the spirometry apparatus could be hidden from investigators. The primary outcome was the incidence of PPC, which was defined as one or more of: pneumonia requiring antibiotics, atelectasis requiring bronchoscopy or respiratory failure requiring ventilatory assistance within 30 days of resection. The incidence of PPC was 12% in the combined treatment group as compared to 13% in those receiving standard PT. Other endpoints and outcomes were similarly unchanged between the groups. The use of IS offers no incremental benefit when added to effective postop PT.

A specifically targeted regimen of postoperative inspiratory muscle training as an add-on to standard PT has also been studied (20). This intervention was able to improve oxygenation as measured by oximetry on postoperative days 3 and 4, but failed to show a decreased incidence of PPC.

A systematic review examining perioperative PT in lung cancer resections was reported (21), which incorporated a total of eight studies. Interventions varied from preoperative interventions, pre- and postoperative interventions and postoperative interventions alone. All studies involved addition of a particular intervention to standard PT (defined as breathing and coughing exercises). The authors concluded that the interventions added to standard PT were not beneficial if only offered in the postoperative period.

Sputum management

Direct airway suctioning

The use of direct bedside airway suctioning to assist with sputum retention in the postoperative period was originally pioneered by Matthews in 1984 in order to avoid intubation or formal tracheostomy insertion (22). He described a 12-Fr mini-tracheostomy cannula, which was inserted percutaneously through the cricothyroid membrane. The technique has been modified, where the preferred insertion site is at the level of the 2nd cartilaginous ring, using bronchoscopic visualization to provide simultaneous tracheobronchial toilet as well as safe and accurate insertion of the cannula.

A 2011 review (23) examined 4 trials involving the use of a minitracheostomy tube in the perioperative setting. This analysis was hampered by the lack of common endpoints between the studies, and one of the studies was purely observational. In only one of the included studies was there rigorous inclusion criteria, and by these criteria are not considered to be high-risk patients. There was a significant reduction in the incidence of sputum retention, which was measured by a variety of endpoints, including (I) number of bronchoscopic procedures performed, (II) incidence of atelectasis (based on chest radiograph report), and (III) incidence of pneumonia. None of the included studies were able to demonstrate that the prophylactic use of a minitracheostomy tube reduced mortality or LOS. Based on the available evidence, which is of limited methodological quality, there appears to be no role for routine use of a minitracheostomy tube in the perioperative period.

Mucolytics

The use of medications to enhance clearance of mucus and secretions has also been examined. Several agents are thought to exert a beneficial effect, including inhaled nebulized hypertonic saline (in the cystic fibrosis population and the collection of induced sputum samples) in addition to mucolytic/expectorant medications. Of these, only the compound ambroxol has been examined in a randomized controlled fashion in the postoperative period after lung resection. This medication promotes decreased secretion and reduced viscosity of mucus via inhibition of secretory pathways. This medication is unfortunately unavailable in North America.

A structured review of seven published studies of ambroxol use in patients undergoing cardiac and thoracic operations was performed (24), specifically comparing high and low dose strategies. In patients undergoing lobectomy, the administration of high-dose ambroxol for 72-h postoperatively (1,000 mg/d intravenously) was associated with significantly reduced rates of PPC (6% *vs.* 19%, P=0.02), shorter LOS (5.6 *vs.* 8.1 days, P=0.02) and decreased hospital costs. A randomized placebo-controlled trial of 140 patients undergoing lobectomy for lung cancer (25) also studied the use of 72 h of 1,000 mg/d ambroxol as compared to standard care. A significant reduction in the rate of PPC (6% *vs.* 19%, P=0.02) and decreased LOS by 2.5 days (P=0.02) was observed when ambroxol was added to routine postoperative care.

While this particular medication is not available worldwide, it can be concluded that the use of mucolytic medications can be effectively used to decrease PPC. Effective sputum clearance has been observed at the Ottawa Hospital with the use of nebulized hypertonic saline (2.5 mL of 3% saline) administered twice daily in addition to chest physiotherapy when sputum retention is noted.

Postoperative respiratory support

Given the risks of developing a PPC after lung cancer resection, the use of non-invasive positive pressure ventilation (NIPPV) or administration of high-flow oxygen delivered by nasal cannula (HFNO) have been explored as modalities to reduce the incidence of PPC.

NIPPV is also referred to by the terms continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP). Both CPAP and BiPAP are administered via nasal/face masks, and exert their beneficial effect by recruitment of collapsed distal airways and alveolar spaces. This leads to improved lung volumes (26), oxygenation and gas exchange (27). In contrast, HFNO which is referred commonly by the trade name of a particular delivery device Maxtech/Optiflow (Fisher & Paykel Healthcare, Laval QC Canada) uses high flow rates of heated and humidified oxygen delivered through a nasal cannula. A low level of positive pressure is generated in the proximal airways as a result of the bulk gas flow. HFNO is thereby thought to enhance sputum clearance, increase tidal volumes (28) and decrease the physiologic dead space (29).

Non-invasive ventilation

A Cochrane review examining the utility of NIPPV after lung cancer resections was completed (30) in 2015. A total of 6 randomized control trials encompassing 436 patients were analyzed. There were significant variations in the actual intervention—NIPPV was used for a variable duration of time (2–14 h) across the studies included, and CPAP was employed in 4 of the 7 studies, with BiPAP for the remainder. Control interventions were not standardized, and included additional treatments such as supplemental oxygen, antibiotics and physical therapy. Outcomes considered in the analysis included overall rate of PPC, rate of re-intubation, mortality, ICU LOS and overall LOS. No difference was identified in the rates of PPC between the control group and those patients receiving NIPPV. The relative risk (RR) was 1.03 with a 95% confidence interval (CI) crossing unity (0.72–1.47). In the three studies reporting rates of reintubation, there was no difference between the groups (RR 0.55; 95% CI: 0.25–1.2). Four studies within the Cochran review that reported mortality rates, showed no difference between the groups (RR 0.6; 95% CI: 0.24–1.53). Finally, there were no differences identified in ICU and overall LOS when NIPPV was used (RR 0.12; 95% CI: 6.1–5.9). The low number of studies that include specific lung cancer patients limits the generalizability of the findings of the Cochrane review. The overall low number of included patients was noted in the study as potentially contributing to a type II statistical error (missing a true difference).

High-flow oxygen

The use of HFNO was examined in a randomized, controlled and blinded study of patients undergoing elective lung resection (31). A total of 59 patients were recruited and assigned to HFNO (n=28) or conventional oxygen therapy (n=31). The primary study outcome was distance achieved in a 6-minute walk test (6MWT), and secondary outcomes included spirometry (FEV_1, FVC), hospital LOS and patient satisfaction. Groups were well-balanced with regards to operative approach (VATS *vs.* open), type of resection (lobectomy *vs.* wedge) and basic demographics. The 6MWT was higher at baseline in the group randomized to HFNO (397 *vs.* 318 m).

This study did not demonstrate a significant improvement in 6MWT or spirometry values with the use of HFNO after elective lung resection. LOS, however, was significantly reduced from a mean of 4 days to 2.5 in the HFNO group. This suggests that the study was likely underpowered relative to its proposed primary endpoint. However, a more pragmatic interpretation is that a composite endpoint such as LOS, which depends on multiple different parameters of care relating to enhanced recovery, may better reflect the positive effects of HFNO in the postoperative period and thus showed an improvement.

A qualitative review (32) examined the literature comparing HFNO with other forms of postoperative support. In all, seven papers were included which accounted for 1,523 patients. The majority of studies included patients from cardiothoracic centres, with only one study reporting on a purely thoracic patient population (from Ansari and colleagues, discussed above), and two reporting a mixed cardiac-thoracic and vascular population. In this analysis, there was heterogeneity of studied outcomes between the included studies—although within those outcomes reported across all studies, significant differences were noted. Oxygenation, as measured by the PaO_2:FiO_2 ratio at 6–12 h postop was improved (261 with HFNO *vs.* 198 in controls). Respiratory rate was only noted to be different in one of the included studies (17 *vs.* 20/min in controls) which is of questionably clinical significance in practice. LOS was reported in four of the included studies, and was only found to be improved with the use of HFNO in one study (discussed above).

The current evidence, as specifically reviewed for patients having undergone lung resection, is unable to inform a best practice recommendation for the use of non-invasive ventilation support in the postoperative setting due to the low number of studies, the lack of standardized interventions and the varied outcomes studied.

Conclusions

Surgical treatment of lung cancer in medically fit patients is considered best treatment, in particular for early-stage disease. Complications do arise, and understanding the identification, prevention and best treatments of these is of paramount importance in the provision of quality surgical care. In this limited review, the best quality data was examined regarding interventions to prevent and treat PPCs. Specific interventions that are currently used to treat PPC were reviewed, and the data underpinning these treatments was outlined. The number of randomized, well-controlled studies was very small, and as such the recommendations contained herein are constrained by this particular lack. Notwithstanding, the following recommendations are made, which we have graded according to the AATS/STS guidelines (33).

Recommendations

(I) When considering patients for surgery, the regular use of a prognostic scoring system facilitates the identification of patients who are at risk of developing PPCs. There are several published schemata, and any validated and accessible scoring schema will be of benefit. The EVAD score has the benefit of being easily calculated based on readily available clinical data, and is the author's recommendation (Class IIb, level B-NR);

(II) Broad-spectrum antibiotics with activity against respiratory flora (such as amoxicillin-clavulate) rather than agents targeted as standard prophylaxis (cephalosporins, vancomycin) for skin infection should be used in order to reduce the risk of developing pneumonia. The use of bronchoscopy at the time of resection to collect sputum samples to guide postoperative therapy could also be considered. There is no data to guide the most appropriate duration of prophylaxis (Class IIa, level B-NR);

(III) Intraoperative OLV must adhere to lung-protective strategies. This includes limiting tidal volumes to less than 6 mL/kg, using PEEP and setting the ventilator to a pressure control setting (Class I, level B-R);

(IV) Chest physiotherapy is essential to avoiding PPC in the postoperative period. Focus should be on deep breathing maneuvers, sputum clearance and enhanced mobility. At present, specific extra interventions such as inspiratory muscle training or incentive spirometry are of no additive benefit (Class I, level B-R);

(V) Sputum clearance can be enhanced by the routine use of mucolytic therapies in the early postoperative period. The specific choice of agent will depend on locally available compounds; ambroxol has been demonstrated to be of benefit in reducing PPC if given during the first 72 h postoperatively (Class IIa, level B-R);

(VI) There is no role for routine airway cannulation such as a minitracheostomy tube for the prevention of sputum retention—the decision to manage sputum retention with direct airway cannulation should be on a case-by-case basis (Class IIb, level C-LD);

(VII) The favourable risk-benefit profile of HFNO should encourage thoracic centres to liberalize its use in those patients who are identified as high-risk or who develop postoperative respiratory distress (Class IIa, level B-R);

(VIII) Finally, the lack of strong supporting evidence should serve to spur further studies of postoperative interventions; efforts can be made to leverage multi-institutional studies, common data definitions and well-characterized and identically implemented treatments. Multicentred studies, constructed with clear inclusion criteria, reproducible interventions and clinically relevant outcomes must be performed to further advance the discovery and optimization of postoperative care after lung resection. Such efforts will serve to bring evidence-based interventions forward for the best care of lung cancer patients undergoing surgical resection (Class I, level C-EO).

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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Supplementary

Search strategy

Database: Ovid MEDLINE(R) ALL <1946 to June 19, 2018>
Search strategy:
1. Pneumonectomy/(24638)
2. exp Lung Neoplasms/su [Surgery] (27878)
3. (Pneumonectom* or pulmonary resect* or lung resect*).ti. (6809)
4. ((lung cancer or lung carcinoma) and (preoperat* or pre operat* or presurg* or pre surg*)).ti. (626)
5. or/1–4 (43507)
6. exp Physical Therapy Modalities/(136645)
7. Spirometry/(19895)
8. Oxygen Inhalation Therapy/(13383)
9. oxygen therapy.tw. (9328)
10. Antibiotic Prophylaxis/(12506)
11. (spirometr* or physiotherap*).ti. (9697)
12. Antibiotic Prophyla*.tw. (8610)
13. 6 or 7 or 8 or 9 or 10 or 11 or 12 (195118)
14. 5 and 13 (871)
15. guideline*.pt. (15966)
16. practice guideline*.pt. (24035)
17. Meta-Analysis.pt. or Meta-Analysis.ti. (111953)
18. review.pt. and systematic.tw. (119203)
19. randomized controlled trial.pt. (465102)
20. random*.ti. (187815)
21. 15 or 16 or 17 or 18 or 19 or 20 (750538)
22. 14 and 21 (83)
23. limit 22 to English language (73)

Database: Ovid MEDLINE(R) ALL <1946 to June 19, 2018>
Search strategy:
1. perioperative care/or preoperative care/(69351)
2. perioperative period/or preoperative period/(7570)
3. (preoperat* or prophyl* or prevent*).tw. (1588752)
4. 1 or 2 or 3 (1628614)
5. Thoracic Surgical Procedures/or pneumonectomy/(30394)
6. thoracic surg*.ti,tw. (13710)
7. (((lung or pulmonary) adj3 (resect* or surg)) or Pneumonectom*).tw. (21095)
8. exp lung cancer/su (27878)
9. or/5–8 (64015)
10. 4 and 9 (9714)
11. Respiratory Insufficiency/pc (939)
12. respiratory failure.tw. (26796)
13. Acute Lung Injury/pc (839)
14. lung injur*.tw. (24434)
15 .11 or 12 or 13 or 14 (50795)
16. 10 and 15 (298)
17. limit 16 to English language (225)
18. limit 17 to yr="2010–Current" (108)