Doi: 10.5152/TJAR.2021.1108

Turkish Journal of Anaesthesiology & Reanimation

Perioperative Anaesthesiological Management of Malignant Pleural Mesothelioma Patients Undergoing Extrapleural Pneumonectomy (EPP) and Extended Pleurectomy/Decortication ((E)PD)

Olivia Lauk[1], Corinna Von Deschwanden[2], Ilhan Inci[1], Claudio Caviezel[1], Isabelle Opitz[1], Bastian Grande[2]

[1]Department of Thoracic Surgery, University Hospital Zurich, Zurich, Switzerland
[2]Institute of Anesthesiology, University Hospital Zurich, Zurich, Switzerland

Cite this article as: Lauk O, Von Deschwanden C, Inci I, Caviezel C, Opitz I, Grande B. Perioperative Anaesthesiological Management of Malignant Pleural Mesothelioma Patients Undergoing Extrapleural Pneumonectomy (EPP) and Extended Pleurectomy/Decortication ((E)PD). *Turk J Anaesthesiol Reanim.* 2021;49(6):494-499.

Abstract

Introduction: Macroscopic complete resection (MCR) within a multimodality treatment concept offers currently the best survival for malignant pleural mesothelioma patients. The current standardised therapy is within a multimodality approach including (neo-)adjuvant chemotherapy followed by macroscopic complete resection (MCR). However, MCR in form of extrapleural pneumonectomy (EPP) or extended pleurectomy/decortication ((E)PD) is correlated with significant morbidity and mortality if not performed in high volume centres as described previously according to the literature. In addition, there exist no standardised anaesthesiological protocol for this surgical approach according to the literature.

Methods: At our institution, diagnosed mesothelioma patients up to an International Mesothelioma Interest Group (IMIG) stage III receive induction chemotherapy followed by either EPP or (E)PD and in certain cases additional adjuvant therapy. In the period 1999–end 2019, 362 patients were intended to be treated and 303 underwent induction chemotherapy followed by MCR. MCR can be achieved either by EPP or (E)PD. Both procedures request a good teamwork between the surgeon and the anaesthesiologist.

Conclusion: Although, there has been a shift lately from EPP towards lung sparing procedure (E)PD, both surgical approaches are still performed to date and is a challenging procedure for both, the surgeon as well as the anaesthesiologist. Herewith, we present our institutional perioperative standard operating procedures for the surgical and anaesthesiological management of EPP or (E)PD according to international terms of reference.

Keywords: Malignant pleural mesothelioma, perioperative guidelines, anaesthesiological management, extrapleural pneumonectomy, extended pleurectomy/decortication

Introduction

Malignant pleural mesothelioma (MPM) patients have a poor overall survival due to a high rate of local recurrence even after multimodality approaches.[1–3] Multimodality therapy approach consisting of chemotherapy combined with macroscopic complete resection (MCR), either extrapleural pneumonectomy (EPP) or extended pleurectomy/decortication ((E)PD), remains the current treatment strategy for resectable MPM. Median time from relapse lies between 3 and 7 months.[1,2] MPM is mainly triggered by asbestos exposure and has a latency period of up to 50 years from primary contact to clinical onset of symptoms. Symptoms as dyspnoea, cough and chest pain are unspecific, but may be the first and leading symptoms. A definite diagnosis must be made by thoracic biopsy. Cytology of suspicious pleural effusion can give a diagnosis; nevertheless, the specificity of cytology is mostly not sufficient to achieve a definitive diagnosis.[4,5]

Although, there has been a shift lately from EPP towards lung sparing procedure, (E)PD, both surgical approaches are still performed to date. The more senior procedure, EPP, includes an en bloc resection of the parietal and

Corresponding Author: Bastian Grande; E-mail: Bastian.grande@usz.ch

Received: 09.09.2020 Accepted: 17.11.2020
Available Online Date: December 17, 2021

visceral pleura combined with the complete lung, as well as the resection of the pericardium and the diaphragm with reconstruction.[4]

(E)PD represents the removal of the parietal and visceral pleura by leaving the lung in place with or without the resection of pericardium/diaphragm. This procedure, especially decortication of the lung, is, compared to EPP, time consuming and makes this intervention complex. There is no standardised protocol for this surgical approach according to the literature. Also important is the fact, that both procedures come along with a moderate mortality and morbidity rate, whereas the mortality rate for EPP is higher than for (E)PD as described in a systematic review by Cao et al.[6] Mortality rates after (E)PD compared to EPP were 2.9 and 6.8%, respectively. Morbidity rates after (E)PD are as high as after EPP, if prolonged air leaks are taken into account, if not, morbidity rates for (E)PD are lower with 27.9% compared to 62.0% undergoing EPP. The overall mortality rate after the multimodality therapy approach ranges from 0 to 11.8%.[7–9] Conclusions regarding the higher mortality rates for EPP show a trend towards the less experienced centres (low-volume centres),[7–9] especially for the postoperative occurrence for acute respiratory distress syndrome.[10–12]

Herewith, we present our institutional perioperative standard operating procedures (SOP) for the surgical and anaesthesiological management of extrapleural pneumonectomy (EPP) or (E)PD according to international terms of reference.

Preoperative Evaluation

Patient Selection

Patient selection, in the sense, of an optimal treatment approach must be predicated on an individual basis, requires expertise, and should be determined in an interdisciplinary tumourboard consisting of specialists from departments of pneumology, oncology, radio-oncology, pathology, radiology, and thoracic surgery.

Main Points

- These institutional standard operating procedures (SOP) should encourage and demonstrate clinicians the importance of the anaesthesiological approach in major malignant pleural mesothelioma surgery based on the decades of institutional experience.
- The surgical and anaesthesiological management in case of EPP or (E)PD can be performed according to institutional guidelines. In individual cases it needs to be adapted to the patient's preoperative condition and the intraoperative course.
- Lung protective ventilation, adapted fluid management (normovolaemia), restrictive transfusion regime, anaesthetic management with short-acting intravenous anaesthetics and prompt postoperative extubation are the most important key factors in the anaesthesiological management for patients with malignant pleural mesothelioma undergoing macroscopic complete resection either by EPP or (E)PD.

The patient's health status and fitness status is important for patient selection and evaluating candidates suitable for surgery. Parameters need to be assessed by pulmonary function test and cardiac assessment.[13] According to the literature, contraindications for patients with certain morbidity profiles do not exist. However, the American College of Cardiology and the American Heart Association (ACC/AHA) guidelines[14] established a 'Revised Cardiac Risk Index' (RCRI) for a better preoperative risk stratification of patients who need further cardiac evaluations. Cause in some cases, further cardiac workup next to a standardised echocardiogram according to these guidelines is mandatory.[13,14] Especially in cases with clinical signs of tachycardia, bradycardia, extrasystoles or known pulmonary hypertension further evaluation with 24 hour-electrocardiogramm (ECG), and transthoracal echocardiography has to be accomplished. An experienced anaesthesiologist must do the clinical evaluation for these patients. Based on these current guidelines, we established an institutional preoperative cardiac risk assessment as shown in Figure 1.

As described earlier, the decision for EPP or (E)PD is made by an interdisciplinary team and the anaesthesiologist and the surgeon accurately evaluate the patient's clinical and cardiopulmonary status according to the patient's comorbidities, tumour volume respectively resectability, and the postoperative remaining pulmonary function and quality of life. This is essential, not only for the postoperative outcome, it also has an impact on the perioperative anaesthesiological management.

The basic preoperative diagnostic tools for the evaluation of a surgical candidate are chest X-ray, computed tomography, positron emission tomography according to European Respiratory Society (ERS) and the European Society of Thoracic Surgery (ESTS) guidelines as well as the IMIG guidelines.[4,15]

Pre-Medication, Installations, and Monitoring

According to our institutional SOPs the patient will be installed with basic monitoring (ECG, noninvasive blood pressure, peripheral venous line, bispectral index measurement [BIS], and muscle relaxation measurement), awake epidural anaesthesia (EDA), asleep arterial, and central venous catheterisation. The EDA should be placed between Th 5-8. There are optional installations such as pulse contour cardiac output (PICCO), pulmonary artery catheterisation, both of which should only be used in exceptional cases. A double luminal endobronchial tubus or optional ipsilateral endobronchial blocker in case double luminal endobronchial tubus is not feasible is mandatory for lung separation during the procedure. The rational for PICCO is not clearly defined due to its limited interpretation for the changing parameters during this operation (first fully perfused pulmonary flow path and after EPP resection reduced flow path in contralateral side placement

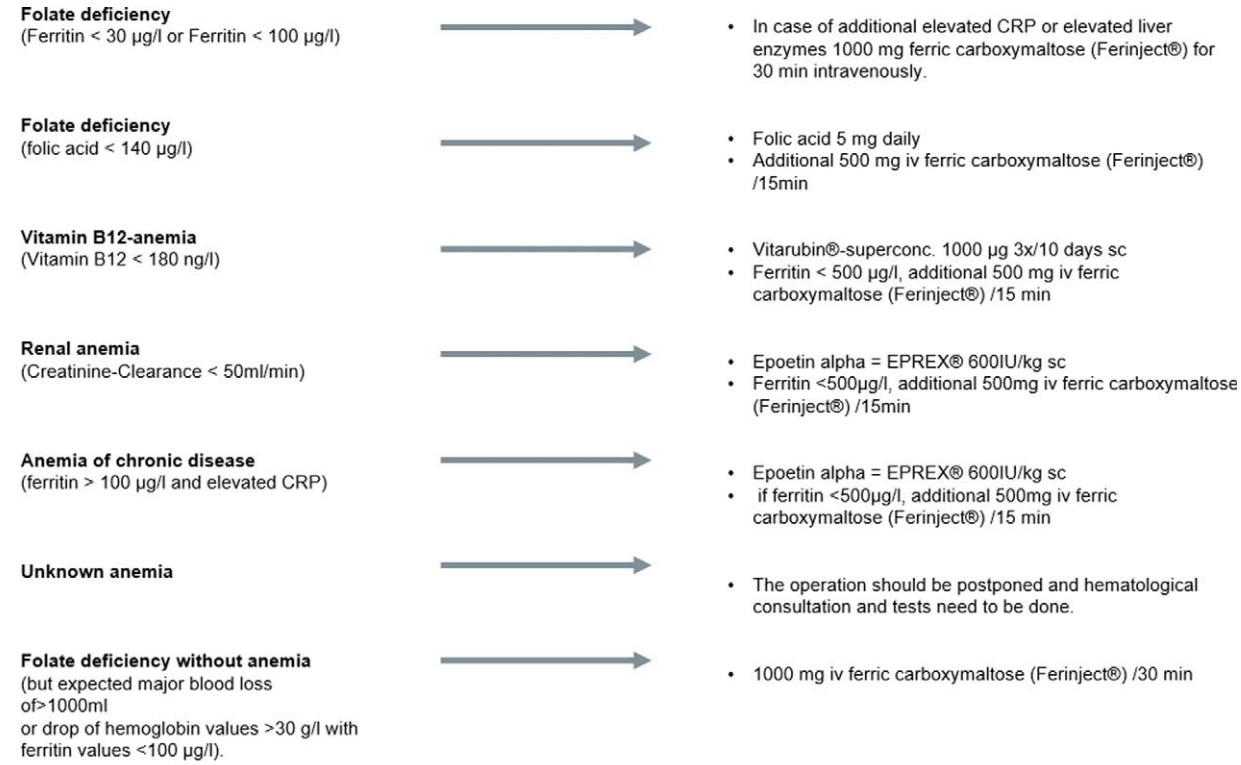

Figure 1. Management of different causes of anemia and therapy.
IV, intravenous; SC, subcutaneous; Min, minutes; CRP, C-reactive protein.

position). Transoesophageal echocardiography should be available pre-, peri-, and postoperatively at all times. In the case of necessity, ilomedin and nitrogen monoxide (NO) need to be prepared and available (Figure 2).

There are a few additional monitoring settings as bispectral index to monitor the depth of anaesthesia, urine catheter due to the length of the operation, and for a better volume monitoring and optional stomach tube for differentiation of the oesophagus from the tumour plane.

The anaesthesia starts with fentanyl or sufentanil as analgetic, propofol in terms of target-controlled infusion and will be followed by rocuronium in normal or rapid sequence induction dosage. Maintenance of the anaesthesia and analgesia with a BIS of 40-55 should be performed with propofol, remifentanil, and via EDA ropivacain 0.33%, 19.8-33 mg h^{-1}. The intraoperative use of EDA is safe, unless it should be reconsidered in cases of hemodynamic instabilities.[16,17] If EDA was not feasible a combination of fentanyl, methadone, propofol as TCI, and rocuronium (high usage: 0.3-0.6 mg kg^{-1} h^{-1}) intravenously and if 'the train of four', an intraoperative monitoring for neuromuscular monitoring, is between <1 out of 4.

The use of inhalation anaesthetics agents should be avoided in (E)/PD, in EPP short-acting inhalation anaesthetics like Desflurane could be used, but there is no evident benefit. Long operation time and intermittent positive end-expiratory pressure (PEEP) for easier decortication can lead to gas exposure in the operation field hence the surgeons may be exposed. In the case of hemodynamic instability reduction of propofol and beginning with midazolam (0.5-2 mg kg^{-1} body weight per hour) are pursued under strict BIS monitoring. In cases with contraindications for propofol as a hypnotic agent (eg, allergies), midazolam should be given continuously and after prior consultation of the surgeon with the risk of prolonged wakening time.

The ventilation should be lung protective throughout the operation. Ventilation should be set with a pressure-controlled mode (PCV), which is preferable to volume-controlled ventilation (whether conventional PVC or volume-guaranteed PCV-VG) (Vt 6-8 mL kg^{-1} body weight; P_{max} < 25 cm H_2O with maximum 30 cm H_2O, PEEP 5 cm H_2O, and permissive hypercapnia, if necessary) as well as low oxygen supply.[18] Protective ventilation has three intraoperative components: Low tidal volume, recruitment manoeuvres (RM), and PEEP. The combined use of these

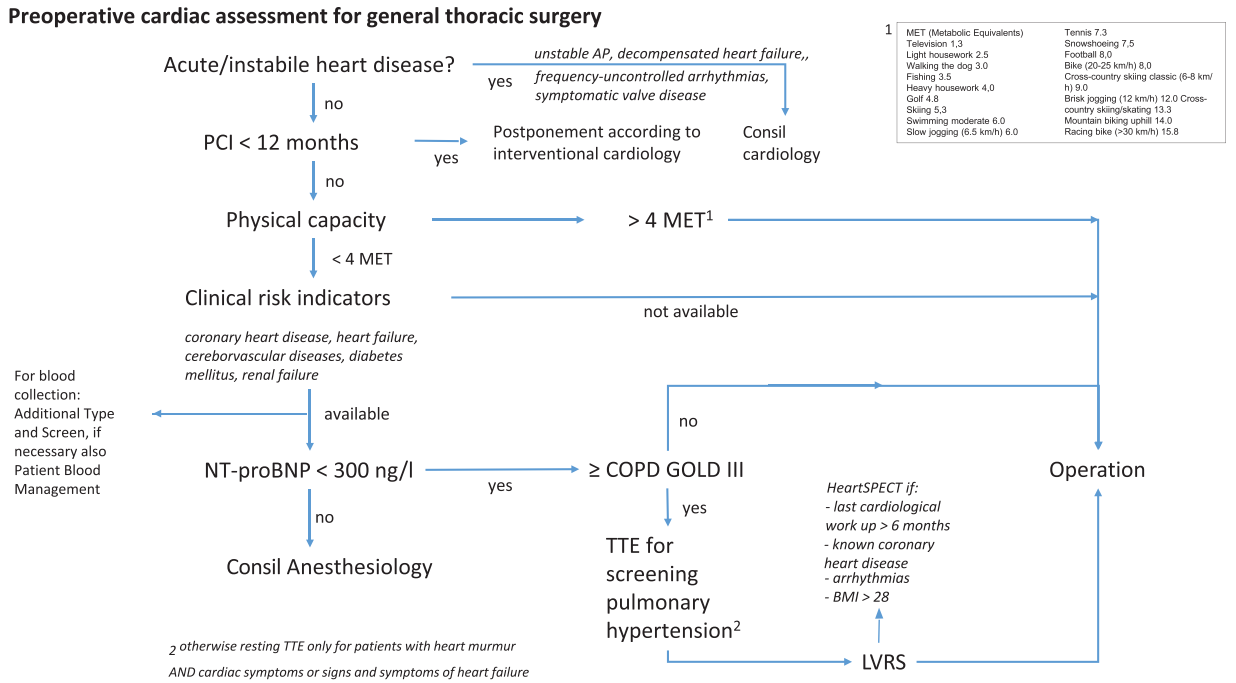

Figure 2. Preoperative cardiac assessment for general thoracic surgery.
PCI, percutaneous coronary intervention; MET, metabolic equivalents; LVRS, lung volume reduction surgery; TTE, transthoracic echocardiogram; AP, angina pectoris; SPECT, single photon emission computed tomography; COPD, chronic obstructive pulmonary disease; BMI, body mass index; NT-proBNP, N-terminal pro brain natriuretic peptide.[13,14]

three components can help prevent both hypoxemia and acute lung injury.[18–20] In the case of induction chemotherapy, as this is the case in the majority of patients, the risk to develop an acute respiratory distress syndrome is very high[11,12,15]; therefore, low PEEP and oxygen supply are essential in the prevention. Immediately after intubation single lung ventilation should be started if pneumothorax, bronchopleural fistula is suspected.

The inspiration:expiration ratio should be chosen individually, to secure a proper expiration, and air trapping should be avoided. The ventilation frequency should be triggered by the arterial CO_2 level ($paCO_2$).

The ventilation of the independent lung should be guided throughout the whole operation with the lowest possible fraction of inspired oxygen (FiO_2) and a positive pressure. This can be measured by arterial O_2 pressure (paO_2), which should be more than 14 kPa or not less than 20% to first paO_2. O_2 uptake can be supported via Ambu breathing bag with PEEP of 5–10 cm H_2O maximum or intermittent ventilation of the dependent lung in close agreement with the surgeons.

At the beginning of the operation, immediately after single lung ventilation, arterial blood gas tests have to be done every 15-30 minutes. This can be switched to 60 minutes controls if there is an acid–base balance and no other noticeable findings.

Volume Management

Volume management is challenging in these surgical procedures due to their long operation hours and huge operation fields with large potential fluid evaporation. On the other hand, the marginal pulmonary status is the limiting factor for excessive volume supply. The standard for such operations should be a basic infusion of 0.5-1.5 ml/kg body weight/h and a compensation of the diuresis of balanced crystalloid infusion. The blood loss should be replaced by balanced colloid infusions, gel or starched based. The volume management can be guided by measurements, although CVP, PiCCO measurements, or even CCO are not very reliable in open chest surgery, by transoesophageal echocardiography, and in the first line by clinical judgement (fullness of the heart).

As there is a higher haematological toxicity for patients after induction chemotherapy, at our institution, the cell saver is standardised used for the surgical interventions. From a quantity of 1000 mL of blood, followed by irradiation, approximately one equivalent of an erythrocyte concentrate of 300 mL are going to be obtained and will be transfused again either during the operation or postoperatively.

Regarding special renal protection mechanism in the case of hyperthermic intrathoracic chemotherapy (HITHOC), which is not applied at our institution, restricted and balanced volume management should be applied. In our phase I study, cisplatin-fibrin was sprayed on the resected surfaces after pleurectomy/decortication, no kidney-damaging dose was detected in serum.[21]

Blood and Coagulation Management

In general, a proper status of the patients' blood and coagulation values are mandatory. In face of the surgical procedure following data need to be collected: A proper bleeding status, medication history of the patient, haemogram, prothrombin time (PT, INR), partial thromboplastin time, fibrinogen, factor V, factor XIII, and 'Rotations-Thromb-Elastogramm'.

In the case of bleeding, erythrocyte concentrates can be given according to institutional guidelines if haematocrit is below 20% and signs of oxygen support deficiency (like new ST-elevation in the ECG, lactacidosis, low-volume-related tachycardia) and the bleeding is ongoing. This decision also has to be discussed in the team because the global outcome of patients given erythrocyte concentrates is poor.[22]

In the case of expected (major, blood loss $\geq$1000 mL or expected drop of haemoglobin $>30\,g\,L^{-1}$) blood loss during the operation preoperative haemoglobin and iron values need to be measured.

In general, all values are valid until 4 weeks pre-operatively.

In the case of normal haemoglobin values the operation can be planned as usual ($>130\,g\,L^{-1}$).

In the case of haemoglobin value of $<100\,g\,L^{-1}$ the operation should be postponed and further haematological tests are required.

In the case of moderate drop ($100\text{-}130\,g\,L^{-1}$) following tests need to be performed: One EDTA tube for haematological tests with differentiation of reticulocytes and one heparin tube for c-reactive protein, creatinine, liver enzymes, lactate dehydrogenase, ferritin, vitamin B12, and folic acid (in the erythrocyte).

In the case of expected major blood loss $\geq$1000 mL or expected drop of haemoglobin $>30\,g\,L^{-1}$ the following tests are needed: Differentiation of reticulocytes, c-reactive protein, creatinine, liver enzymes, lactate dehydrogenase, ferritin, vitamin B12, and folic acid (in the erythrocyte).

In the case of different causes of anaemia, we recommend the following therapy schema[22]:

Post-operative Care

All patient should be extubated immediately after surgery. To avoid extended coughing, we recommend changing the double lumina tube to a laryngeal mask in deep anaesthesia, transferring the patient into spontaneous breathing, and extubate him afterwards. Regardless of the chosen surgical procedure, fast postoperative extubation always is mandatory for faster postoperative pulmonary recovery. The chest tube after (E)PD needs a suction of -5 cm H_2O, and after EPP, it has to be clamped and just opened once per 8 hours for bleeding control as well as to avoid luxation of the heart.

If an extubation is not possible, the tube should be changed from the LMA into a single lung tube under fibroscopical vision to avoid aspiration related complications.

The surgical and anaesthesiological procedure for EPP and (E)PD is highly individual and should be adapted to the preoperative condition of the patient and the intraoperative procedure. Nevertheless, there are basic principles of treatment that we strongly recommend: (1) lung protective ventilation, (2) adapted fluid management (normovolaemia), (3) restrictive transfusion regime, (4) anaesthetic management with short-acting intravenous anaesthetics, and (5) prompt postoperative extubation.[1]

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - O.L., I.O., B.G.; Design - O.L., I.O., B.G.; Supervision - I.O., B.G. Resource - O.L., I.O., B.G..; Materials - n.a..; Data Collection and/or Processing - O.L., I.I., C.C., I.O..; Analysis and/or Interpretation - O.L., C.C., B.G.; Literature Search - O.L., B.G.; Writing - I.O., C.v.D., I.I., C.C., I.O., B.G. ; Critical Reviews - C.v.D., I.I., C.C.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Baldini EH, Recht A, Straus GM, et al. Patterns of failure after trimodality therapy for malignant pleural mesothelioma. *Ann Thorac Surg.* 1997;63(2):334-338. [CrossRef]
2. Kostron A, Friess M, Crameri O, et al. Relapse pattern and second-line treatment following multimodality treatment for malignant pleural mesothelioma. *Eur J Cardiothorac Surg.* 2016;49(5):1516-1523. [CrossRef]
3. Soldera SV, Kavanagh J, Pintilie M, et al. Systemic therapy use and outcomes after relapse from preoperative radiation and extrapleural pneumonectomy for malignant pleural mesothelioma. *Oncologist.* 2019;24(7):e510–e517.
4. Baas P, Fennell D, Kerr KM, et al on behalf of the ESMO Guidelines Committee*. Malignant pleural mesothelioma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2015;26(Supplement5):v31-v39. [CrossRef]

5. Sayan M, Eren M, Gupta A, et al. Current treatment strategies in malignant pleural mesothelioma with a treatment algorithm. *Adv Respir Med*. 2019;87(5):289-297. [CrossRef]
6. Cao C, Tian D, Park J, et al. A systematic review and meta-analysis of surgical treatments for malignant pleural mesothelioma. *Lung Cancer*. 2014;83(2):240-245. [CrossRef]
7. Rusch VW, Rosenzweig K, Venkatraman E, et al. A phase II trial of surgical resection and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. *J Thorac Cardiovasc Surg*. 2001;122:788-795. [CrossRef]
8. Hasani A, Alvarez JM, Wyatt JM, et al. Outcome for patients with malignant pleural mesothelioma referred for trimodality therapy in Western Australia. *J Thorac Oncol*. 2009;4:1010-1016. [CrossRef]
9. Branscheid D, Krysa S, Bauer E, et al. Diagnostic and therapeutic strategy in malignant pleural mesothelioma. *Eur J Cardiothorac Surg*. 1991;5:466-472; discussion 473. [CrossRef]
10. Sharkey AJ, Bilancia R, Tenconi S, et al. Extended pleurectomy decortication for malignant pleural mesothelioma in the elderly: The need for an inclusive yet selective approach. *Interact Cardiovasc Thorac Surg*. 2017;25(5):696-702. [CrossRef]
11. Burt B, Cameron R, Mollberg N, et al. Malignant pleural mesothelioma and the society of thoracic surgeons database: An analysis of surgical morbidity and mortality. *J Thorac Cardiovasc Surg*. 2014;148:30-35. [CrossRef]
12. Weder W, Stahel RA, Bernhard J, et al.; Swiss Group for Clinical Cancer Research. Multicenter trial of neo-adjuvant chemotherapy followed by extrapleural pneumonectomy in malignant pleural mesothelioma. *Ann Oncol*. 2007;18:1196-1202. [CrossRef]
13. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (writing committee to revise the 2002 guidelines on perioperative cardiovascular evaluation for noncardiac surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol*. 2007;50(17):e159–e241.
14. Fleisher LA, Fleischmann KE, Auerbach AD, et al. ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol*. 2014;64:e77–e137.
15. Opitz I, Scherpereel A, Berghmans T, et al. ERS/ESTS/EACTS/ESTRO guidelines for the management of malignant pleural mesothelioma. *Eur J Cardio-Thorac Surg*. 2020;58:1-24. [CrossRef]
16. Lederman D, Easwar J, Feldman J, et al. Anesthetic considerations for lung resection: Preoperative assessment, intraoperative challenges and postoperative analgesia. *Ann Transl Med*. 2019;7:356-356. [CrossRef]
17. Sudheshna KD, Gopinath R, Ayya SS, et al. High vs mid thoracic epidural analgesia—A comparative study on the ease of insertion and effects on pain, hemodynamics, and oxygenation in patients undergoing thoracotomies. *Ann Card Anaesth*. 2019;22:383-387. [CrossRef]
18. Grande B, Ganter MT. What is the best strategy for one-lung ventilation during thoracic surgery? *J Thorac Dis*. 2018;10:6404-6406. [CrossRef]
19. Grande B, Loop T. Anaesthesia management for bronchoscopic and surgical lung volume reduction. *J Thorac Dis*. 2018;10:S2738-S2743. [CrossRef]
20. Senturk M, Slinger P, Cohen E. Intraoperative mechanical ventilation strategies for one-lung ventilation. *Best Pract Res Clin Anaesthesiol*. 2015;29:357-369. [CrossRef]
21. Opitz I, Lauk O, Meerang M, et al. Intracavitary cisplatin-fibrin chemotherapy after surgery for malignant pleural mesothelioma: A phase I trial. *J Thorac Cardiovasc Surg*. 2020;159:330-340. [CrossRef]
22. Spahn DR, Goodnough LT. Alternatives to blood transfusion. *Lancet*. 2013;381(9880):1855-1865. [CrossRef]