Contemporary Surgical Management of Advanced End Stage Emphysema: An Evidence Based Review

Anand Sachithanandan, FRCSI (CTh), Balaji Badmanaban, FRCSI (CTh)

Cardiothoracic Surgery Division, Serdang Hospital, Jalan Puchong, Kajang, Selangor 43000, Malaysia

SUMMARY

Emphysema is a progressive unrelenting component of chronic obstructive pulmonary disease and a major source of mortality and morbidity globally. The prevalence of moderate to severe emphysema is approximately 5% in Malaysia and likely to increase in the future. Hence advanced emphysema will emerge as a leading cause of hospital admission and a major consumer of healthcare resources in this country in the future. Patients with advanced disease have a poor quality of life and reduced survival. Medical therapy has been largely ineffective for many patients however certain subgroups have disease amenable to surgical palliation. Effective surgical therapies include lung volume reduction surgery, lung transplantation and bullectomy. This article is a comprehensive evidence based review of the literature evaluating the rationale, efficacy, safety and limitations of surgery for advanced emphysema highlighting the importance of meticulous patient selection and local factors relevant to Malaysia.

KEY WORDS:
Emphysema, Lung volume reduction surgery, Lung transplantation

INTRODUCTION

Emphysema is a progressive unrelenting condition which is a component of the spectrum of chronic obstructive pulmonary disease (COPD). Physiologically it is characterized by severe airflow limitation with resulting hyperinflation. Pathologically the emphysematous element of COPD refers to a permanent dilatation of the air sacs distal to the terminal bronchioles secondary to alveolar wall destruction but without fibrosis. Put simply, the emphysematous lung requires less pressure to inflate, but once inflated exerts less emptying pressure than a normal lung. In the advanced stages of the disease, the remodeling of the peripheral lung unit and thoracic cavity results in an increased work of breathing as the ventilatory mechanics of the chest wall and diaphragm become less efficient.

COPD is significantly underdiagnosed worldwide including here in Malaysia [1]. Estimates from the World Health Organization (WHO) Global Burden of Disease Study, predict that by 2020, the projected year by which Malaysia should hopefully attain fully developed industrialized high income nation status, COPD will account for the 3rd largest cause of global deaths and be the fifth commonest cause of loss of disability adjusted life years (DALYs) [2]. Based on the prevalence of the main aetiological risk factors of cigarette smoking and air pollution, it is estimated the prevalence of moderate to severe emphysema (using the Global Initiative for Chronic Obstructive Lung Disease -GOLD criteria) within the adult population (> 30 yrs age) in Malaysia is approximately 4.55% [3]. This is hardly surprising given the high prevalence of smoking amongst adult males in the country which is approaching 50% [4]. Hence it is not unreasonable to expect COPD to emerge as a leading cause of hospital admissions and a major economic burden on the healthcare resources in this country in the future.

Patients with advanced emphysema have a poor quality of life (QOL) with restricted mobility, often have a requirement and dependence on domiciliary long term oxygen therapy (LTOT) and have a reduced survival. Patients with a FEV1 < 30% of predicted values have a reduced median survival of 40-50% at only three years [5-8]. This dismal prognosis is similar to the natural history of severe symptomatic aortic valvular stenosis or untreated severe left main coronary artery disease. However in contrast, these latter two patient groups usually receive prompt life saving treatment.

Rationale for Surgery & Historical Origins

Medical therapy for advanced emphysema includes short and long acting beta-agonists and anti-cholinergic bronchodilator therapy, oral or inhaled corticosteroid therapy, methylxanthines, phosphodiesterase (PDE4) inhibitors, antibiotics, pneumococcal and influenza vaccination, LTOT, smoking cessation, nutritional support, pulmonary rehabilitation and non-invasive ventilation. However for a significant proportion of patients, medical therapy has been largely ineffective in halting the progression of this debilitating disease. Because of the increased mortality and reduced QOL seen with severe emphysema, multiple surgical treatments have been devised.

From the start of the last (20th) century, a plethora of surgical procedures have been attempted including costochondrectomy, transverse sternotomy, thoracoplasty and phrenectomy, pneumoperitoneum and local lung excision with plication for bullous disease. With the exception of bullae excision, all other interventions have been discarded due to lack of proven benefit, an associated high mortality or for non reproducibility.

Lung Volume Reduction Surgery (LVRS)

The precursor to contemporary lung volume reduction

This article was accepted: 26 March 2012
Corresponding Author: Anand Sachithanandan, Cardiothoracic Surgery Division, Serdang Hospital, Jalan Puchong, Kajang, Selangor 43000, Malaysia
Email: anandsachithanandan@yahoo.com

surgery (LVRS) can be traced back to 1957 when Brantigan performed a wedge excision to decrease lung volume and reduce dyspnea[9]. By downsizing the lung, Brantigan hoped to increase both the radial and circumferential traction on the airways resulting in a more rapid and complete expiratory flow, and improve the chest wall and diaphragmatic ventilatory mechanics. His early results demonstrated good clinical improvement but was associated with an unacceptably high peri-operative mortality (18-20%) and the procedure was soon abandoned[9].

Contemporary LVRS resurfaced three decades later with Joel Cooper's seminal publication reporting an impressive 82% improvement in mean FEV1 (from 0.77 L to 1.4 L) for a select group of COPD patients who underwent bilateral LVRS[10]. The contemporary surgical principles were essentially unchanged from Brantigan's era with the goals of resecting non-functioning hyperinflated areas of the lung, reduce the degree of hyperexpansion, improve lung elastic recoil resulting in a more rapid and complete expiratory flow and improve the mechanics of ventilation.

Patient selection & NETT

Patient selection is of paramount importance for successful LVRS. Following publication of Cooper's impressive results in 1993, there was a proliferation of cardiothoracic centers and surgeons who carried out similar operations but with varying results. Small patient numbers, variable selection criteria, non randomized case-controlled series, incomplete follow-up, a lack of long-term data and reporting bias, all collectively confounded meaningful interpretation of the clinical data regarding the safety and efficacy of this operation. The proliferation of LVRS procedures at non-specialized centers resulted in poor outcomes with high mortality and re-hospitalization rates of 23% and 40% respectively at 12 months follow-up[11]. For an elective operation designed primarily to palliate patients with advanced end stage emphysema such outcomes were clearly unacceptable. The cardiothoracic and respiratory community acknowledged that a randomized study with a controlled, non-surgical arm was both ethically supportable and scientifically essential and this took shape in the form of the North American National Emphysema Treatment Trial (NETT).

The NETT trial was a multi-center prospective randomized clinical trial (RCT) that provided level 1 evidence on the safety and efficacy of LVRS and importantly NETT identified which COPD patient subgroups would benefit from an LVRS procedure and in which patients was the operation contraindicated[12]. In summary, 1218 patients with predominantly advanced emphysema and significant, largely irreversible air flow limitation (FEV1< 45%) and hyperinflation (TLC> 110% and RV > 150%) were randomized to optimal medical therapy in addition to LVRS (surgical group) or just isolated optimal medical therapy (medical group), upon completion of 6-10 weeks of a supervised pulmonary rehabilitation programme. Both patient groups continued to receive pulmonary rehabilitation therapy following randomization.

Four COPD patient subgroups emerged from the NETT data analysis, stratified according to the anatomical distribution of the emphysema and baseline pre-operative post pulmonary rehabilitation exercise tolerance (ET). NETT also identified two high risk sub groups: patients with severe disease (predicted FEV1 < 20% and predicted DLCO < 20% and/or homogenous disease) and patients with non-upper (UL) lobe disease and a high baseline ET, who fared poorly with surgery. LVRS in these patients was associated with a high mortality and minimal functional benefit[12]. In contrast, patients with heterogenous disease; predominantly UL emphysema and a low baseline ET had excellent symptomatic, spirometric and functional benefit over similar patients treated medically. This subgroup also had a significant prognostic benefit compared to the medical group with an improved survival on follow up at two years[12]. The remaining two subgroups – patients with UL disease and a high ET, and non-UL disease with low ET also reported significant symptomatic and functional improvement but surgery conferred no survival advantage over medical therapy.

Pre-operative investigations

The NETT trial illustrated the importance of careful patient selection hence all potential LVRS patients require a methodical pre-operative work-up which includes a detailed history and examination, Alpha-1-antitrypsin levels, chest radiograph, high resolution computed tomography (CT) scan, quantitative V/Q scan, full pulmonary function tests including lung volume measurements (with body plethysmography), arterial blood gases, and functional exercise testing (eg. 6 minute walk test, shuttle walk test, cardiopulmonary stress test with VO2 max calibration). Co-existing ischaemic heart disease (IHD) is not uncommon in emphysema patients and a left heart study may be required to exclude concomitant coronary artery disease. Approximately 70% of COPD patients in Malaysia have at least one significant co-morbidity and almost 25 % have coexisting IHD. Elevated estimated pulmonary arterial pressures on echocardiography may require formal interrogation with a right heart study as pulmonary hypertension is a contraindication for LVRS.

Surgical Technique & Considerations

A variety of surgical techniques have been successfully employed for LVRS. The traditional "open" approach utilizes a median sternotomy or posterolateral thoracotomy. Alternatively, LVRS can be performed with a minimally invasive video assisted thoracoscopic (VATS) approach. Currently no RCT data exists to support the efficacy or superiority of either approach although a VATS procedure may have a lower incidence of respiratory failure[13]. In reality, individual surgeon preference and expertise usually determines how the LVRS operation is performed. Controversy also exists as to whether a unilateral or bilateral procedure is better. Again no RCT data is available although most retrospective studies suggest a bilateral procedure has better outcomes, probably reflecting the bilateral nature of advanced emphysema.

Different techniques including laser and stapling have been used to resect the hyperinflated diseased lung segments however stapled wedge resections have unequivocally become the current gold standard of care. In a randomized trial of laser versus stapling in 72 COPD patients who had bilateral LVRS, McKenna et al identified a higher incidence of delayed pneumothorax, increased need for supplemental oxygen and a reduced FEV1 at 6 months with laser resections [17].

Reinforced staple lines have been shown to be superior in terms of a reduced incidence of air leaks facilitating earlier chest drain removal and potentially shorter hospital stay. Suture lines can be reinforced with polytetrafluoroethylene (PTFE), bovine pericardium or collagen strips. Endoscopic staplers with pre-mounted reinforcement strips (eg. Covidien Duet TRS Endo GIA stapler) are now commercially available further enhancing the thoracic surgeon's armamentarium. However judicious use of reinforcement strips is required when dealing with younger LVRS patients who may become lung transplant recipients in the future as these strips can evoke intense inflammatory adhesions which may render explantation of the native lung at a future transplant more difficult.

Contemporary results of LVRS

Ginsburg *et al* recently reported excellent early and midterm results with no operative or 90-day deaths in 49 patients who underwent bilateral LVRS [18]. The patients in this series were selected based on the NETT criteria (all had UL disease) with either high or low ET. All patients demonstrated significant improvements in the parameters of the BODE index, a multidimensional functional measure of COPD severity. This contemporary study strongly suggests that in appropriate patients, LVRS can be performed with a low surgical risk and provide excellent midterm results, reiterating the importance of careful patient selection.

Alternative surgical therapy I - Lung transplantation

Lung transplantation remains the gold standard treatment for a subset of COPD patients with advanced emphysema. Emphysema and alpha-1 anti trypsin deficiency are the most common indications for adult lung transplantation worldwide and account for 61.2% of single lung transplants (SLT) and 32.1% of bilateral lung transplants (BLT) globally [19]. The advantages of a lung transplant are obvious with a complete replacement of the diseased non-functioning lung resulting in dramatic symptomatic, physiologic and functional improvements for the recipient, usually eliminating the need for domiciliary LTOT. Although most emphysema patients have a relatively stable course whilst awaiting a donor lung, in the USA the median waiting time is currently approximately 2 years but this is likely to increase. New regulations (introduced in 2005) governing the allocation of donor organs have legislated that potential transplant recipients be prioritized according to clinical need rather than time spent on the waiting list. How this will impact on outcomes of future lung transplants for emphysema patients remains to be determined. Statistics on local waiting times here in Malaysia are less easily available. Excellent results have been reported in leading transplant centers with 1 and 5 year survival rates of 88% and 59% respectively (Washington University data) [20].

Disadvantages of transplantation are numerous including the need for lifelong immunosuppression and a relatively high incidence of chronic allograft dysfunction or rejection which approaches 50% at 5 years [21]. This has been attributed to the development of bronchiolitis obliterans (BO), a major cause of late (> 1 year) mortality post transplantation. BO is a cicatricial process affecting the respiratory and terminal bronchioles, resulting in fibrosis and obliteration of airway lumens. Ischaemia-reperfusion injury (IRI) is a more acute problem and correlates with an increased risk of acute rejection. IRI is a significant cause of early morbidity and mortality following lung transplantation but can be attenuated with use of inhaled nitric oxide to decrease pulmonary arterial pressures thereby facilitating a more controlled reperfusion.

Long term immunosuppression increases the risk of neoplasm formation, accelerated coronary artery atherosclerosis and an increased susceptibility to infection. The transplant operation is not without risk and most series report a 30-day mortality of 5-15% [19]. Lung transplantation is also an expensive therapy with the need for long term surveillance and biopsies, and some might argue this does not constitute optimal use of limited healthcare resources. However the biggest limitation is the lack of available donors. Improvements in road safety have depleted the pool of available donor organs globally although locally, motor vehicle accidents were the third commonest cause of hospitalization in Malaysia in 2008 [22]. The scarcity of donor lungs is further exacerbated here in Malaysia due to cultural indifference and misperception regarding organ donation. Interestingly, most studies suggest better outcomes for BLT over a SLT with improved 5 year survival rates for BLT. This has been attributed in part to the lower incidence of BO with BLT [19,20,23]. However, the limited available pool of donor lungs mandates optimal use of this scarce resource; a pair of lungs from a single donor may potentially be better utilised for two different SLT recipients. In short, although lung transplantation is an imperfect solution and a relatively infrequent therapy here in Malaysia, for a certain subset of COPD patients with advanced disease it still offers the best palliation and some prognostic benefit. A legislative change to assumed consent (requiring active 'opting out') may be necessary to optimize availability of organs but this has legal and ethical considerations, which is beyond the scope or intent of this review.

Ideal Surgical Therapy: LVRS Versus Transplantation or both

In contrast to transplantation, there is no waiting list for an LVRS procedure. The operation can be performed on appropriately selected patients once they have successfully completed a 6-12 week course of pulmonary rehabilitation. It is comparatively inexpensive and no immunosuppression is required. Most published series report a lower operative mortality rate of 3-8% and additionally unlike lung transplantation which is rarely offered to patients over the age of 65 years, there is no age criteria per se for a LVRS procedure. However LVRS is not the panacea for all patients with advanced end stage emphysema requiring surgery. The operation benefits only a highly selected group of patients as documented in the NETT trial. High risk patients with extreme limitation of pulmonary function, patients with diffuse homogenous emphysema, and alpha 1 antitrypsin deficiency patients are better served with a transplant or continued maximal medical therapy. The success of a LVRS procedure is also dependant and limited by the anatomical and pathological state of the patient's own lungs.

In real life practice, lung transplantation and LVRS are not competing therapies as each operation caters to a different

Table I: Local Selection Criteria for LVRS

Indications	**Clinical Criteria** . Severe COPD with predominantly emphysema . Marked dyspnoea despite maximal medical therapy . Patient motivated and willing to undergo pulmonary rehabilitation (minimum 6 weeks pre-operatively) . Poor exercise tolerance /quality of life **Physiologic Criteria** . Airflow obstruction ie. FEV_1 < 35-40% . TLCO < 60% *However FEV1/TLCO must NOT be < 20% **Radiological Criteria** . Hyperinflation (flattened hemi-diaphragms) on CXR . Predominantly upper lobe (UL) disease ie. heterogenous emphysema on HRCT
Contra-indications	. Age > 70 years . Hypercapnia . Pulmonary hypertension . Still smoking . Alpha-1 Anti-trypsin deficiency . Severe co-morbidity . Very severe airflow limitation ie. FEV_1/TLCO < 20% . Homogenous diffuse global emphysema or lower lobe (LL) emphysema
Essential Investigations	. Spirometry . 6-minute walk test or equivalent exercise test . CXR . CT scan (preferably HRCT) . Arterial blood gas (ABG) analysis . Echocardiogram +/-Right heart catheter . Alpha-1 Anti-trypsin deficiency blood test/screen

patient subgroup. Infact, LVRS can be used as a bridge to transplantation and palliate the patient's symptoms whilst awaiting a donor lung. The expected duration of sustained benefit from LVRS is approximately 2-5 years. Importantly, a prior LVRS procedure does not appear to have any detrimental impact on the course or prognosis of a future lung transplant. In a retrospective analysis of 791 COPD patients who underwent a SLT or BLT, including 50 (6.3%) patients with a prior LVRS, Nathan et al reported no difference in operative mortality, hospital stay, post-transplant late graft dysfunction or 1 year survival [24]. However, difficult decisions arise when dealing with patients of a certain age threshold (for example a 62 years-old patient) in whom the palliative benefits of an LVRS may render them no longer a candidate for a future transplant several years later due to advanced age.

Another permutation is a simultaneous SLT and LVRS procedure to treat contralateral native lung hyperinflation and this may be an effective hybrid strategy in some cases [25]. Early post-SLT unilateral LVRS is another rare option to treat contralateral native lung hyperinflation and has resulted in superior pulmonary function over solitary SLT historical controls [26]. In the context of Malaysia, based on our review of the existing literature, we have included useful local criteria for LVRS patient selection (Table I).

Alternative surgical therapy II - Bullectomy

A subset of COPD patients with predominantly emphysematous bullous disease may benefit from a bullectomy. A bullae is defined as a markedly dilated (> 1 cm) air space within the lung parenchyma and is thought to arise from a ball-valve mechanism. Sizeable bullae increase the physiological dead space and may exert a compressive effect on the underlying normal lung tissue. The natural history is one of progressive enlargement with worsening dyspnea. A giant bullae is one that occupies at least one third of the ipsilateral hemithorax. The bullae is lined by respiratory epithelium and most of the outer surface made of visceral pleura. Bullous disease can be classified based on the anatomy of the bullae and the quality of the underlying lung and this may be useful to evaluate surgical candidates and predict functional outcome. One classification scheme is as follows:

Group I: Single large bulla with underlying normal lung
Group II: Multiple bullae with underlying normal lung
Group III: Multiple bullae with underlying lung diffusely emphysematous
Group IV: Multiple bullae with underlying lung affected by other diseases

Patients in Group I and II are ideal surgical candidates with predictably good results. Patients in Group III and IV must be carefully selected as functional results and clinical outcome are less predictable. Indications for bullectomy include patients with a giant bullae (occupying 1/3 to 1/2 of the hemithorax) with or without severe dyspnea, or to treat associated complications including a secondary spontaneous pneumothorax, pain, haemoptysis or recurrent infection. Surgery is contraindicated in patients who continue to smoke

or those with significant co-morbidities. Pulmonary hypertension, poorly defined bullae (on radiological imaging), advanced age, hypercapnia and cor pulmonale are other contraindications to surgery. A bullectomy can be performed via an "open" technique usually a thoracotomy (staged or simultaneous bilateral) or sternotomy. Alternatively a VATS approach may be feasible in some cases. The bullae is resected under general anaesthesia with a double lumen endotracheal tube to facilitate single lung ventilation. It may be excised with an endoscopic stapler or plicated. With plication, instead of resecting the bulla, it can be rolled or folded over itself, placing a stapler across the base. This facilitates reinforcement of the staple line with the bullae itself. However most thoracic surgeons prefer to excise a bullae due to the associated risk of an occult malignancy [27]. A key decision for the surgeon is determining how much lung to resect in addition to the bullae as the goal of achieving a healthy secure staple line must be balanced with the need to avoid excessive or unnecessary resection of healthy lung parenchyma.

The modified Monaldi or Brompton technique though rarely performed is an alternative technique which involves placement of a concentric purse-string suture in the lateral wall of the bullae via a small CT guided incision. Catheter drainage of the bullae with talc insufflation elicits a fibrous reaction and promotes a rapid and permanent contraction of the cavity. Talc is then also insufflated around the free pleural space to induce pleurodesis. The pleural drainage catheter is usually removed within 48 hours and the intra-bullae catheter within 8 days [28].

If the bullae has destroyed or replaced much of the lung parenchyma then an anatomical resection (segmentectomy or lobectomy) may be required. Complications of a bullectomy include post-operative air leak, a residual intrathoracic pleural space, atrial fibrillation, pulmonary embolism, pneumonia and respiratory failure requiring mechanical ventilation. The operation carries a mortality of up to 7% in most published series [29-31]. Currently no RCT data exists regarding the efficacy of a giant bullectomy however data from numerous case series and uncontrolled observational studies suggests that a significant and sustained functional and symptomatic improvement (up to 5 years) can be achieved in a majority (60-90%) of carefully selected patients [28,30-32]. The choice between a VATS or open approach, similar to a LVRS procedure, is determined primarily by surgeon preference and technical expertise.

Future (non-surgical) therapies

A range of bronchoscopic techniques such as endobronchial blockers, airway bypass, endobronchial valves, thermal vapor ablation, biological sealants and airways implants are currently being investigated as possible future therapies [34]. Although subjective improvements in dyspnea status and QOL seem to be frequently documented, current available data on the efficacy of these various endoscopic modalities remains inconclusive and will require time for a thorough evaluation. Hybrid therapy combining contemporary surgery, maximal medical treatment and minimally invasive bronchoscopic techniques may be a feature of future treatment strategies.

CONCLUDING REMARKS

The prevalence of moderate to severe emphysema is approximately 5% in Malaysia and this is likely to increase in the future given the high national prevalence of cigarette smoking. Patients with advanced disease have a poor QOL and reduced survival. Medical therapy is largely ineffective for many patients however their disease may be amenable to surgical palliation. Lung volume reduction surgery (LVRS), lung transplantation and bullectomy are three different but well established effective surgical therapies for appropriately selected patients with advanced end stage emphysema.

Meticulous patient selection and methodical peri-operative care with emphasis on comprehensive pulmonary rehabilitation is fundamental for a good surgical outcome. The latter unfortunately is only currently offered in a few hospitals and more supervised rehabilitation programmes need to be developed in Malaysia. Primary care physicians and respiratory specialists should be aware of the efficacy and limitations of these operative procedures which form an integral part of the spectrum of available contemporary local treatment modalities for the management of advanced medically refractory end stage emphysema.

REFERENCES

1. Regional COPD Working Group. COPD prevalence in 12 Asia-Pacific countries and regions: projections based on the COPD prevalence estimation model. Respirology 2003; 8: 192-8.
2. Murray CJL, Lopez AD. The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries and Risk Factors in 1990 and Projected to 2020. Harvard University Press, Cambridge, MA, 1996.
3. Regional COPD Working Group. Trends in COPD mortality and hospitalizations in countries and regions of Asia-Pacific. Respirology 2009; 14: 90-7.
4. Report of the Second National Health and Morbidity Survey Conference 1997, Public Health Institute, Ministry of Health, Malaysia.
5. Diener CF, Burrows B. Further observations on the course and prognosis of chronic obstructive pulmonary disease. Am Rev Respir Dis 1975; 111: 719-24.
6. Traver GA, Cline MG, Burrows B. Predictors of mortality in chronic obstructive pulmonary disease. Am Rev Respir Dis 1979; 119: 895-902.
7. Burrows B, Earle RH. Course and prognosis of chronic obstructive lung disease: a prospective study of 200 patients. N Engl J Med 1969; 280: 397-404.
8. Nocturnal-Oxygen-Therapy-Trial –Group. Continous or nocturnal oxygen therapy in hypoxaemic chronic obstructive lung disease. Ann Intern Med 1980; 93: 391-8.
9. Brantigan OC, Kress MB, Mueller EA. The surgical approach to pulmonary emphysema.1961. Chest 2009; 136 (5 Suppl) pp e30.
10. Cooper JD, Trulock EP, Triantafillou MDA, Patterson GA, Pohl MS, Deloney PA, Sundaresan RS, Roper CL. Bilateral pneumectomy (volume reduction) for chronic obstructive pulmonary disease. J Thorac Cardiovasc Surg 1995; 109 (1): 106-16.
11. Department of Health and Human Services. Report to Congress: Lung volume reduction surgery and Medicare coverage policy: Implications of recently published evidence. 1998
12. Fishman A, Martinex F, Naunheim K, Piantadosi S, Wise R, Ries A *et al.* A randomized trial comparing lung volume reduction surgery with medical therapy for severe emphysema. New Eng J Med 2003; 348(21): 2059-73.
13. Kotloff RM, Tino G, Bavaria JE, Palevsky HI, Hansen-Flaschen J, Wahl PM, Kaiser LR. Bilateral lung volume reduction surgery for advanced emphysema. A comparison of median sternotomy and thoracoscopic approaches. Chest 1996; 110 (6): 1399-406.
14. McKenna RJ, Brenner M, Fischel RJ, Gelb AF. Should lung volume reduction for emphysema be unilateral or bilateral ? J Thorac Cardiovasc Surg 1996; 112 (5): 1331-8.
15. Kotloff RM, Tino G, Palevsky HI, Hansen-Flaschen J, Wahl PM, Kaiser LR, Bavaria JE. Comparison of short term functional outcomes following unilateral and bilateral lung volume reduction surgery. Chest 1998; 113(4): 890-5.

16. Serna DL, Brenner M, Osann KE, McKenna RJ, Chen JC, Fischel RJ, Jones BU, Gelb AF, Wilson AF. Survival after unilateral versus bilateral lung volume reduction surgery for emphysema. J Thorac Cardiovasc Surg 1999; 118(6): 1101-9.
17. McKenna RJ, Brenner M, Gelb AF, Mullin M, Singh N, Peters H, Panzera J, Calmese J, Schein MJ. A randomized prospective trial of stapled lung reduction versus laser bullectomy for diffuse emphysema. J Thorac Cardiovasc Surg 1996; 111(2): 317-21.
18. Ginsburg ME, Thomashow BM, Yip CK, DiMango AM, Maxfield RA, Bartels MN, Jellen P, Bulman WA, Lederer D, Brogan FL, Gorenstein LA, Sonett JR. Lung Volume reduction surgery using the NETT selection criteria. Ann Thorac Surg 2011; 91: 1556-61.
19. Trulock EP, Edwards LB, Taylor DO, Boucek MM, Keck BM, Hertz MI. The registry of the International Society for Heart and Lung Transplantation: twenty-second official adult lung and heart-lung transplant report-2005. J Heart Transplant 2005; 24: 956-67.
20. Lau CL, Meyers BF. Lung volume reduction surgery in the candidate for lung transplantation. Difficult decisions in Thoracic Surgery: An Evidenced-Bsaed Approach. Ed: Ferguson MK. 2007 1st edition 175-85.
21. Sundaresan S, Trulock EP, Mohanakumar T, Cooper JD, Patterson MDG and The Washington University Lung Transplant Group. Prevalence and outcome of bronchiolitis obliterans syndrome after lung transplantation. Ann Thorac Surg 1995; 60(5): 1341-7.
22. Ministry of Health Malaysia. Annual Report 2008. KAB Communication Sdn Bhd 2008; 13.
23. Hadjiliadis D, Davis RD, Palmer SM. Is transplant operation important in determining post transplant risk of bronchiolitis obliterans syndrome in lung transplant recipients ? Chest 2002; 122: 1168-75.
24. Nathan SD, Edwards LB, Barnett SD, Ahmad S, Burton NA. Outcomes of COPD Lung transplant recipients after lung volume reduction surgery. Chest 2004; 126: 1569-74.
25. Todd TRJ, Perron J, Winton TL, Keshavjee SH. Simultaneous single-lung transplantation and lung volume reduction. Ann Thorac Surg 1997; 63: 1468-70.
26. Kroshus TJ, Bolman RM, Kshettry VR. Unilateral volume reduction after single-lung transplantation for emphysema. Ann Thorac Surg 1996; 62: 363-8.
27. Venuta F, Rendina EA, Pescarmona EO, De Giacomo T, Vizza D, Flaishman I, Ricci C. Occult lung cancer in patients with bullous emphysema. Thorax 1997; 52: 289-90.
28. Shah SS, Goldstraw P. Surgical management of bullous emphysema: experience with the Brompton technique. Ann Thorac Surg; 58: 1452.
29. Palla A, Desideri M, Rossi G et al. Elective surgery for giant bullous emphysema: a 5-year clinical and functional follow-up. Chest 2005; 128: 2043.
30. Neviere R, Catto M, Bautin N et al. Longitudinal changes in hyperinflation parameters and exercise capacity after giant bullous emphysema surgery. J Thorac Cardiovasc Surg 2006; 132: 1203.
31. Schipper PH, Meyers BF, Battafarano RJ *et al*. Outcomes after resection of giant emphysematous bullae. Ann Thorac Surg 2004;78: 976.
32. Celli BR, MacNee W, ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004; 23: 932.
33. Ernst A, Anantham D. Bronchoscopic Lung volume reduction. Semin Thorac Cardiovasc Surg 2010; 22(4): 330-7.