Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Transplantation Reviews 37 (2023) 100772

Contents lists available at ScienceDirect

Transplantation Reviews

journal homepage: www.elsevier.com/locate/trre

Review article

Current and future role of double-lung transplantation for bilateral lung cancer

Jeeyeon Lee [a,b,1], Samuel J. Schellenberg [a,1], Liam Il-Young Chung [a], Ankit Bharat [a,**], Young Kwang Chae [a,*]

[a] Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
[b] School of Medicine, Kyungpook National University, Kyungpook National University Chilgok Hospital, Daegu, Republic of Korea

ARTICLE INFO

Keywords:
Double lung transplantation
Lung cancer
Bilateral

ABSTRACT

Technological advances have progressively enhanced the survival rate of lung transplant recipients and expanded its indications for various diseases, including the recent coronavirus disease 2019 (COVID-19). However, according to the International Society for Heart and Lung Transplantation, lung cancer constituted a mere 0.1% of the indications for lung transplantation over the past two decades. This statistic has remained stagnant, and numerous lung cancer patients continue to be excluded from lung transplantation candidacy. Contrary to the general exclusion of lung cancer patients from transplantation, the post-transplant survival rate for these patients is not inferior to that of patients with non-cancerous diseases. Furthermore, lung transplantation may offer curative treatment for patients with bilateral lung cancer whose respiratory insufficiency has advanced independently of cancer progression. This review aims to elucidate and examine the role of double lung transplantation (DLT) in bilateral lung cancer. We summarize the established indications for lung transplantation, appropriate histologic or molecular subtypes of lung cancer for transplantation, technical advances to minimize recurrence, post-DLT survival outcomes for lung cancer patients, and related translational research. We suggest that although DLT for bilateral lung cancer presents challenges, it may be considered a potential treatment option in select circumstances.

1. Introduction

Lung transplantation has evolved as a successful therapeutic option for patients with end-stage lung disease over the decades. Since Dr. Hardy's pioneering lung transplantation attempt for lung cancer in 1963 [1], advancements in technology and medical management have broadened surgical expertise and indications for lung transplantation. In the last two decades, significant enhancements in recipient selection, immunosuppressive agents, and surgical techniques have contributed to its widespread adoption. Notably, survival rates have improved, double-lung transplantation (DLT) has become twice as common as single-lung transplantation (SLT), and respiratory failure due to coronavirus disease 2019 (COVID-19) has emerged as a new indication for lung transplantation [2,3]. Despite these advancements, lung cancer has represented a mere 0.1% of indications for lung transplantation over the past 20 years [4].

Since 2010, the 1- and 5-year survival rates for adult lung transplantation have increased to 85% and 59%, respectively [5,6]. However, the 5-fold higher risk of developing lung malignancies post-transplantation compared to the general population and the 13-fold elevated risk of cancer development in the native lung after SLT have led to physicians' reluctance to utilize lung transplantation for lung cancer patients [7–10]. Additionally, no prospective study has compared survival outcomes between conventional oncologic treatments and transplantation for lung cancer, nor has there been a systematic review of post-transplantation survival outcomes. As a result, lung transplantation for lung cancer has been restricted to select patients, such as those with early-stage lung cancer or histologically

* Corresponding author at: Department of Internal Medicine (Hematology and Oncology), Feinberg School of Medicine, Northwestern University, 645 N. Michigan Ave, Suite 1006, Chicago, IL 60611, USA.
** Corresponding author at: Department of Thoracic Surgery, Feinberg School of Medicine, Northwestern University, Arkes Pavilion, 676 N St Clair St Ste 2140, Chicago, IL 60611, USA.
E-mail addresses: ankit.bharat@nm.org (A. Bharat), YCHAE@nm.org (Y.K. Chae).
[1] These authors equally contributed to this work.

https://doi.org/10.1016/j.trre.2023.100772

Available online 17 June 2023

confirmed bronchioloalveolar carcinoma (BAC) [11–15], while stage IV lung cancer is generally considered a contraindication (Table 1) [16]. Despite these limitations, advancements in surgical techniques and the development of perioperative management protocols have facilitated ongoing exploration of lung transplantation for lung cancer (Fig. 1) [17–21].

This article aims to (1) elucidate the role of DLT in bilateral lung cancer by examining current practices and survival outcomes of DLT for lung cancer, (2) explore the potential future role of DLT for lung cancer, (3) highlight the importance of appropriate candidate selection for DLT to enhance successful outcomes.

2. Methods

We used the terms "Lung cancer", "Double or Bilateral" and "Transplantation" to search articles published in PubMed and EMBASE without any date limitations. A total of 140 and 260 articles were initially retrieved in PubMed and EMBASE, respectively, excluding 183 duplicates. After screening the titles and abstracts, research articles and case series related to bilateral or DLT for lung cancers were manually identified. Publications on metastatic lung cancer ($n = 9$) and incidental lung cancer ($n = 14$) as well as those that did not meet the selection criteria ($n = 6$), an article not published in English (n = 1), a commentary (n = 1), and a letter to the editor (n = 1) were excluded. A total of 8 case series and 74 eligible publications related to DLT for lung cancer were reviewed and summarized in this study (Fig. 2).

3. Indications for lung transplantation

3.1. Lung transplantation for lung cancer

The main indications for lung transplantation have been chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, or pulmonary fibrosis usually due to interstitial pneumonia and rarely sarcoidosis, histiocytosis and connective tissue-related disease, cystic fibrosis, α1-anti-trypsin deficiency emphysema, and idiopathic pulmonary arterial hypertension [22–26]. Although lung cancer as an indication for lung transplantation had increased from 19 cases (0.1% of total) in 2006 to 32 cases (0.1% of total) in 2010 [27,28], it accounted for only 0.1% of the total lung transplantation cases during the last two decades (Table 2) [17,29,30]. Furthermore, according to the data provided by the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS), the frequency of DLT for lung cancer was approximately 0.11% between 2011 and 2020 [31]. However, lung transplantation could serve as an alternative treatment approach for lung cancer refractory to systemic therapies, where the cancer does not respond to standard treatments, including immunotherapy, chemotherapy, radiation, or targeted therapy [21].

The first DLT was performed in 1986 on a patient who had an emphysema [32]. Since 2002, the annual number of DLTs has exceeded that of SLTs, with cystic fibrosis being the most common indication for DLT between 1987 and 2007 [22]. However, according to the 2015 annual report of the International Society of Heart and Lung Transplantation (ISHLT), COPD became the most common indication for DLT, whereas bronchiectasis associated with cystic fibrosis and interstitial lung disease were reported as the second and third most common indications, respectively, similar to SLT [33]. As the indications for lung transplantation continued to broaden, several cases of DLT for lung malignancy had been reported [11,14,15,34–36]. According to these publications, around 40%–50% of recipients experienced lung cancer recurrence after DLT, with the transplanted lung being the most common recurrence site [12–15,34]. Despite the relatively higher risk of tumor recurrence after lung transplantation, lung transplantation has still been considered owing to its acceptable survival outcomes. Notably, the 5-year overall survival (OS) and cancer-specific survival (CSS) rates of patients who received lung transplantation for lung cancer are approximately 39%–57% and 50%–86%, respectively [12,13,34].

The primary objective of cancer surgery is the complete removal of

Table 1
Summary of published case reports regarding double-lung transplantation for lung cancer.

Authors	Year	No. of patients	Histology of tumor	Use of cardio-pulmonary bypass	Recurrence (n, %)	Initial recurred site	Recurrence-free survival (range, mo)	Overall survival (range, mo)	Overall survival rate (%)	Cancer-specific survival rate (%)
Etienne et al. [11]	1997	1	BAC[a]	Unknown	0/1 (0.0)		65	65	5-year 100.0	5- year 100.0
Garver et al. [15]	1999	5	BAC	Yes	3/5 (60.0)	Donor lung ($n = 3$)	10–50	10–50	2-year 60.0	2-year 60.0
Payolan et al. [14]	2000	2	BAC	Yes (n = 1) No ($n = 1$)	1/2 (50.0)	Donor lung (n = 1)	9, 16	16, 48	2-year 50.0	2-year 100.0
Zorn et al. [34]	2003	7	BAC	Yes ($n = 5$) No (n = 2)	4/7 (57.1)	Donor lung (n = 3) Brain, Bone (n = 1)	9–76	15–89	2-year 74.1 5-year 57.1	2-year 83.3 5-year 66.6
de Perrot et al.[c] [12]	2004	Single ($n = 9$) Double ($n = 17$)	BAC	Yes ($n = 21$) No (n = 5)	13/26 (50.0); 5-yr 35.0%	Donor lung ($n = 11$) Others (n = 2)	5–29	11–82	5-year 39.0 10-year 31.0	81.8[#]
Ahmed et al.[c] [13]	2012	Single (n = 6) Double ($n = 23$)	BAC (n = 14) BAC + ADC[b] (n = 11) ADC (n = 2) Unknown ($n = 2$)	Unknown	–	–	–	–	5-year 57.0 10-year 25.0	83.0[d]
Wang et al. [35]	2012	1	BAC	No	0/1 (0.0)		12	12	1-year 100.0	1-year 100.0
Zhang-Velten et al. [36]	2020	1	Lepidic predominant ADC	Unknown	1/1 (100.0)	Donor lung (n = 1)	17	144	12-year 100.0	12-year 100.0

[a] Bronchioloalveolar carcinoma.
[b] Adenocarcinoma.
[c] It was not possible to distinguish between patients who underwent single- or double-lung transplantation for lung cancer.
[d] The period of cancer-specific survival was not identified.

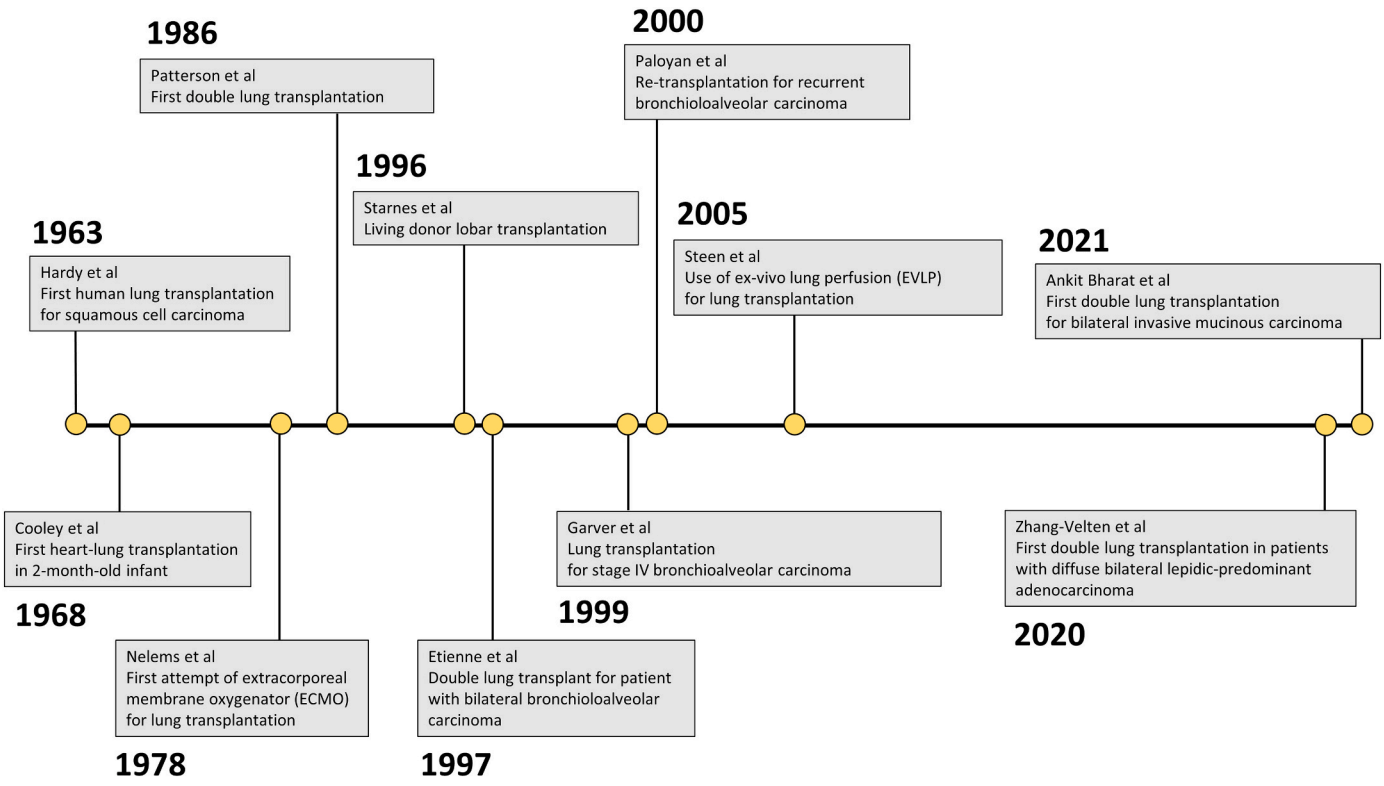

Fig. 1. History of lung transplantation.

the cancerous tissue. Pneumonectomy is considered in situations where extensive multifocal disease or diffuse cancers render limited resections unfeasible [12]. Consequently, bilateral pneumonectomy, in concept, constitutes the radical removal of all pulmonary disease, and when combined with DLT, can be employed for bilateral diffuse lung cancers that are resistant to systemic therapies. However, these patients should not have extrapulmonary disease or regional nodal metastasis prior to lung transplantation (Fig. 3) [37].

3.2. Histology of lung cancer for lung transplantation

Considerations for lung transplantation encompass not only the extent of disease but also the histologic subtype of lung cancer. Initially, the 2007 report on evidence-based clinical practice guidelines published by the American College of Chest Physicians did not regard lung transplantation as a therapeutic option for BAC [38]. However, the most recent update from the ISHLT stated that adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) of the lung may be accepted as special disease considerations when conventional medical therapies fail [39]. Lung transplantation should be reserved for lung-limited AIS, MIA, lepidic predominant adenocarcinoma, or unresectable diffuse cancer that is refractory to oncologic treatments [37,40]. Furthermore, invasive mucinous carcinoma (IMA) tends to present with multicentric or multilobar opacities, consolidation, and bilateral involvement [41]. Consequently, bilateral IMA of the lung with respiratory failure may also be considered an indication for DLT.

Given its generally poorer oncologic outcomes compared to other lung cancer subtypes, IMA has not been traditionally considered an indication for lung transplantation [42,43]. However, oncologic outcomes can vary depending on the distinct phenotypes of IMA [44–49]. While several studies reported worse prognosis for IMA patients than non-IMA patients [50,51], one study on the prognosis of IMA in the lungs found no significant difference in overall survival (OS) between IMA and non-IMA cases [52]. Furthermore, two other studies revealed that resectable and stage IV IMAs exhibited better OS than non-IMAs with similar characteristics [53,54]. These inconsistent results may be attributed to prognostic differences among IMA phenotypes or the presence of prognosis-related factors such as spread through air spaces (STAS) or mucin-producing characteristics [44,55–58]. Additional research on histology-related prognosis or prognosis-related factors could help identify more suitable candidates for lung transplantation and broaden the indications for this procedure.

3.3. Survival outcomes after DLT in lung cancer

According to data from the OPTN/UNOS, patients with BAC/cancer had a 5- and 10-year graft survival rate of 44% and 19%, respectively; however, their OS rate was higher (5-year OS, 57%; 10-year OS, 25%). Although lung cancer has been regarded as an unfavorable indication for lung transplantation owing to poor survival outcomes, the long-term OS of patients who received lung transplantation for lung cancer was not inferior to that of patients undergoing transplant for other indications (HR = 1.11, $p = 0.665$) [13]. ISHLT and OPTN/UNOS data have shown similar trends, with a 5- and 10-year OS rate of 39% and 31% after lung transplantation for lung cancer, respectively (Table 2) [12]. Moreover, other case series have shown a 5-year OS rate of 20%–100% after lung transplantation for lung cancer [11,15,34,36]. Available evidence suggests that as follow-up periods increase, the survival difference between lung cancer and noncancer patients who had received lung transplantation decreases. Earlier enrollment of patients with lung cancer as candidates for lung transplantation, when their condition is still much better, can improve survival rates.

An analysis of survival rates after lung transplantation according to whether patient received DLT or SLT revealed a significant difference between the two groups. Notably, patients in the DLT group showed superior 5- and 10-year survival outcomes than those in the SLT group (DLT group: 3-year, 24.9%; 5-year, 19.6%; SLT group: 3-year, 44.6%; 5-year, 32.5%) [33]. A comparison of post-transplant lung cancer between the DLT and SLT groups revealed that the incidence of post-transplant lung cancer was significantly greater in the latter (9/131, 6.9%) than

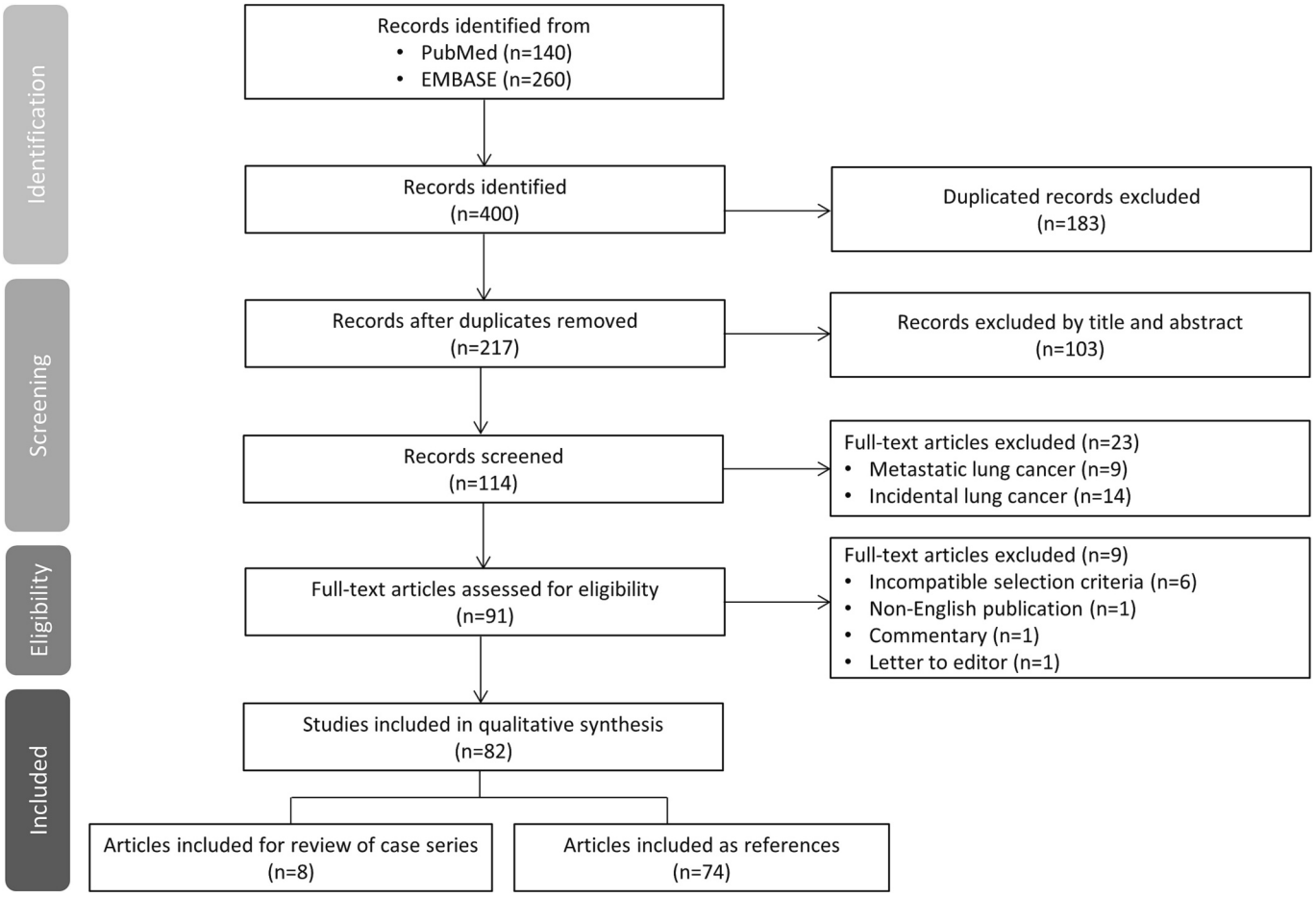

Fig. 2. Flow diagram for selecting eligible publications.

in the former (0/131, 0%; $p = 0.002$) [59]. Another study found that longer follow-up periods resulted in greater differences in survival rates between the DLT and SLT groups [22]. These findings suggest that DLT is more beneficial than SLT [7,60,61].

Furthermore, a study on lung transplantation for lung cancer found that survival outcomes were better with DLT than with SLT. Moreover, reports showed that the 2- and 5-year OS of SLT for lung cancer was 50%, whereas those of DLT for lung cancer were 60% and 57%, respectively [15,34]. In the overall case series, the 2-, 5-, and 10-year OS rates after DLT for lung cancer were 50%–74%, 39%–100%, and 25%–31%, respectively [11–15,34].

Several case series found that the cancer-specific survival (CSS, 50%–86%) was slightly higher than the overall survival (OS) in patients who received DLT for lung cancer [12,34], whereas recurrence rates varied from 0% to 75% (8-year survival after bilateral lung transplantation for BAC of the lungs) [11,12,14,15,34,62]. The most common site for tumor recurrence after lung transplantation for lung cancer is the transplanted donor lung, and the characteristics of recurrent tumors are very similar to those of the recipient's explanted lung [13,15]. This suggests that the recurrence originates not from the donor but from residual tumor components entering into the air space or the residual respiratory system. Therefore, further studies should investigate technical and therapeutic strategies for improving survival outcomes after lung transplantation for lung cancer.

3.4. Advances in surgical techniques for DLT in lung cancer

The current surgical approach of lung transplantation includes a technique of sequential lung transplantation. Using this approach, the worst lung is typically replaced first followed by the second. This technique requires airway anastomosis at the levels of each main bronchus. A unique advantage of this technique is the possible avoidance of cardiopulmonary bypass (CPB). Although several studies have supported the use of CPB [63–65], there are concerns associated with it use which include bleeding, early graft dysfunction, acute-phase reaction of protease cascades, leukocyte and platelet activation resulting in tissue injury, and endothelial damage by increasing capillary permeability or pulmonary edema [66–69]. The technique of sequential lung transplant provides the flexibility regarding the use of CPB unlike the en bloc double lung transplant in which both lungs have to be simultaneously removed necessitating CPB [32,65].

Most DLTs are now performed as a sequential procedure, with CPB generally not being used. Importantly, during the sequential DLT technique, after one side of the lung is resected, ipsilateral lung transplantation is performed while maintaining ventilation with the remaining lung. Thereafter, the contralateral lung is removed while maintaining ventilation using the transplanted lung. During each single-lung ventilation, malignant cells can potentially spread from the diseased lung into the newly transplanted lung. Indeed, in the published reports, local recurrence seems to occur most frequently in the first lung implanted. Further support of this mode of transmission stems from the fact that most lung cancer recurrences are detected in the donor's lung and not in extrathoracic organs and show molecular patterns similar to that of the initial lung cancer [15,70]. Therefore, for the purposes of lung transplantation for patients with cancer, we advocate the use of bilateral pneumonectomy using CPB first and then implanting both new lungs sequentially.

To avoid using CPB, several studies have proposed the use of

Table 2
Type of lung transplantation, indication, and overall survival of patients who received double-lung transplantation (DLT) for lung cancer based on data from the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) and International Society of Heart and Lung Transplantation (ISHLT).

Variables		OPTN/UNOS data (%)		ISHLT data (%)
Type of lung transplantation [17,80]	Double-lung transplantation	63.69	Double-lung transplantation	65.58
	Single-lung transplantation	36.31	Single-lung transplantation	34.42
Indication of DLT [17,22]	Cystic fibrosis	32.83	Chronic obstructive pulmonary disease	31.89
	Chronic obstructive pulmonary disease	11.04	Bronchiectasis	27.38
	Idiopathic pulmonary fibrosis	6.72	Interstitial lung disease	24.01
	Primary pulmonary hypertension	3.51	Pulmonary arterial hypertension	6.09
	Lung cancer	0.10	Lung cancer	0.09
	Others	22.09	Others	41.34
Overall survival (OS) [12,13,81,82]	DLT for noncancer disease	5-year OS 50 10-year OS 27	DLT for noncancer disease	5-year OS 50 10-year OS 35.3
	DLT for lung cancer	5-year OS 57 10-year OS 25	DLT for lung cancer	5-year OS 39 10-year OS 31

*Although some data may have been duplicated in the OPTN and ISHLT registry, it was impossible to distinguish.

extracorporeal membrane oxygenation (ECMO) [71]. Since CPB requires full-dose heparin while ECMO uses low-dose or no heparin, multiple studies have reported significantly lower post-transplant complication rates in groups utilizing ECMO [72,73]. The intraoperative ECMO group experienced fewer transfusions, fewer reoperations, and a lower incidence of bleeding and early graft dysfunction compared to the CPB group. Although the 1-year and 3-year mortality rates for recipients who received DLT were higher in the no-ECMO group than in the ECMO group ($p = 0.016$, $p = 0.020$) [74], the 90-day mortality rate was only 3.1%, and 2-year survival was 86% when intraoperative ECMO was used during DLT. Nonetheless, there was no significant difference between recipients who used CPB or ECMO. While ECMO might be potentially associated with lower bleeding risks, if bilateral pneumonectomy is performed, the recipient will require a full dose of anticoagulation, as the heart must be entirely bypassed while the lungs are implanted. This is necessary since outflow from the right ventricle is divided following the bilateral pneumonectomy and is not restored until at least one lung is implanted and the pulmonary circulation to that lung is opened. Hence, CPB might be better suited for the DLT for recipients with cancer.

3.5. Translational research in DLT for lung cancer

New technologies and advances in the field of lung cancer may impact transplant care for lung cancer patients. With the improvement in surgical technique and post-operative management, the long-term survival following lung transplantation have greatly improved. Lung transplantation could be a highly impactful treatment option for carefully selected patients with medically refractory treatment cancers limited to the lungs. The very early stages of lung cancer or recurrence can be identified by calculating changes in the levels of circulating tumor DNA (ctDNA) or other biomarkers [75–77]. Translational studies using ctDNA are being actively conducted not only for the early detection of lung cancer and its recurrence but also in the field of post-transplant lymphoproliferative disorder, a common post-transplant malignancy in heart and lung transplant recipients [78,79]. These studies can contribute to increasing the success rate of lung transplantation in lung cancer. However, further translational studies are required to determine the role of lung transplantation as a curative

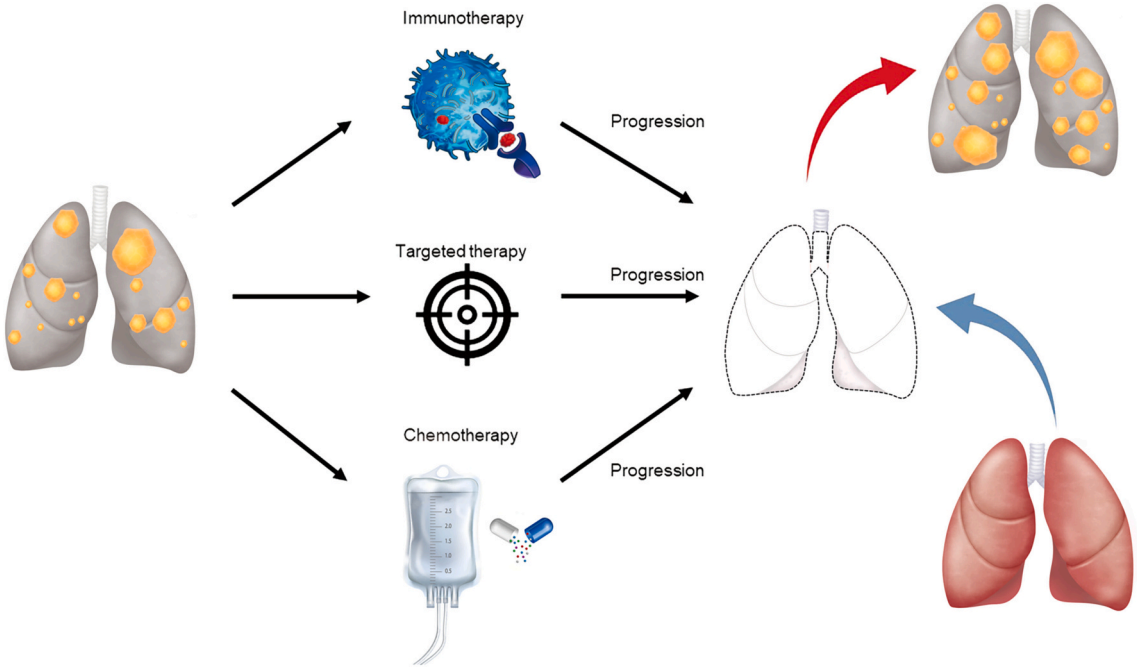

Fig. 3. Treatment process of bilateral lung cancer up to double-lung transplantation (DLT). When conventional medical therapies fail and progression to respiratory failure is observed in patients with bilateral lung cancer confined to both lungs, DLT can be considered for curative treatment.

treatment for lung cancer.

4. Conclusions and future directions

This review demonstrated that DLT has the potential to be a treatment option for patients with bilateral lung cancer refractory to systemic therapies and who have progressed to respiratory failure. Although the performance rate of lung transplantation for lung cancer has been only 0.1% for 20 years, evidence suggests that lung cancer patients who received lung transplantation showed acceptable survival outcomes.

Recent advances in surgical and medical technologies for lung transplantation have contributed significantly to increasing the success rate of lung transplantation. To date, however, the status and histologic characteristics of lung cancer as an indication for DLT have been restrictive, preventing us from exploring the potential role of DLT as a treatment option for bilateral lung cancer. This could be addressed by identifying a special protocol to improve the survival outcomes of patients with bilateral lung cancer, which should differ from the general protocol for lung transplantation. Achieving this will require several additional studies that evaluate associated clinical and pathologic factors.

Funding

This work was supported by NIH grants (USA) HL145478 (to Ankit Bharat).

CRediT authorship contribution statement

Jeeyeon Lee: Conceptualization, Methodology, Investigation, Writing – review & editing, Visualization. **Samuel J. Schellenberg:** Writing – review & editing, Supervision. **Liam Il-Young Chung:** Investigation. **Ankit Bharat:** Data curation, Writing – review & editing, Visualization, Project administration. **Young Kwang Chae:** Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration.

Declaration of Competing Interest

The authors have no conflicts of interest.

Acknowledgment

Not applicable.

References

[1] Hardy JD, Webb WR, Dalton ML, Walker GR. Lung homotransplantation in man. JAMA 1963;186:1065–74. https://doi.org/10.1001/jama.1963.63710120001010.
[2] Chambers DC, Perch M, Zuckermann A, Cherikh WS, Harhay MO, Hayes D, et al. The international thoracic organ transplant registry of the International Society for Heart and Lung Transplantation: thirty-eighth adult lung transplantation report - 2021; focus on recipient characteristics. J Heart Lung Transplant 2021;40:1060–72. https://doi.org/10.1016/j.healun.2021.07.021.
[3] Bharat A, Querrey M, Markov NS, Kim S, Kurihara C, Garza-Castillon R, et al. Lung transplantation for patients with severe COVID-19. Sci Transl Med 2020;12:eabe4282. https://doi.org/10.1126/scitranslmed.abe4282.
[4] Goldfarb SB, Hayes D, Levvey BJ, Cherikh WS, Chambers DC, Khush KK, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Twenty-first Pediatric Lung and Heart–Lung Transplantation Report-2018; Focus theme: multiorgan transplantation. J Heart Lung Transplant 2018;37:1196–206. https://doi.org/10.1016/j.healun.2018.07.021.
[5] Rana A, Godfrey EL. Outcomes in solid-organ transplantation: success and stagnation. Tex Heart Inst J 2019;46:75–6. https://doi.org/10.14503/THIJ-18-6749.
[6] Bos S, Vos R, Van Raemdonck DE, Verleden GM. Survival in adult lung transplantation: where are we in 2020? Curr Opin Organ Transplant 2020;25:268–73. https://doi.org/10.1097/MOT.0000000000000753.
[7] Mathew J, Kratzke RA. Lung cancer and lung transplantation: a review. J Thorac Oncol 2009;4:753–60. https://doi.org/10.1097/JTO.0b013e31819afdd9.
[8] Engels EA, Pfeiffer RM, Fraumeni JF, Kasiske BL, Israni AK, Snyder JJ, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA 2011;306:1891–901. https://doi.org/10.1001/jama.2011.1592.
[9] Pérez-Callejo D, Torrente M, Parejo C, Laporta R, Ussetti P, Provencio M. Lung cancer in lung transplantation: incidence and outcome. Postgrad Med J 2018;94:15–9. https://doi.org/10.1136/postgradmedj-2017-134868.
[10] Triplette M, Crothers K, Mahale P, Yanik EL, Valapour M, Lynch CF, et al. Risk of lung cancer in lung transplant recipients in the United States. Am J Transplant 2019;19:1478–90. https://doi.org/10.1111/ajt.15181.
[11] Etienne B, Bertocchi M, Gamondes JP, Wiesendanger T, Brune J, Mornex JF. Successful double-lung transplantation for bronchioalveolar carcinoma. Chest 1997;112:1423–4. https://doi.org/10.1378/chest.112.5.1423.
[12] de Perrot M, Chernenko S, Waddell TK, Shargall Y, Pierre AF, Hutcheon M, et al. Role of lung transplantation in the treatment of bronchogenic carcinomas for patients with end-stage pulmonary disease. J Clin Oncol 2004;22:4351–6. https://doi.org/10.1200/JCO.2004.12.188.
[13] Ahmad U, Wang Z, Bryant AS, Kim AW, Kukreja J, Mason DP, et al. Outcomes for lung transplantation for lung cancer in the united network for organ sharing registry. Ann Thorac Surg 2012;94. https://doi.org/10.1016/j.athoracsur.2012.04.069. 935–40; discussion 940–941.
[14] Paloyan EB, Swinnen LJ, Montoya A, Lonchyna V, Sullivan HJ, Garrity E. Lung transplantation for advanced bronchioloalveolar carcinoma confined to the lungs. Transplantation 2000;69:2446–8. https://doi.org/10.1097/00007890-200006150-00041.
[15] Garver RI, Zorn GL, Wu X, McGiffin DC, Young KR, Pinkard NB. Recurrence of bronchioloalveolar carcinoma in transplanted lungs. N Engl J Med 1999;340:1071–4. https://doi.org/10.1056/NEJM199904083401403.
[16] Weill D. Lung transplantation: indications and contraindications. J Thorac Dis 2018;10:4574–87. https://doi.org/10.21037/jtd.2018.06.141.
[17] Yusen RD, Edwards LB, Dipchand AI, Goldfarb SB, Kucheryavaya AY, Levvey BJ, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-third adult lung and heart-lung transplant Report-2016; focus theme: primary diagnostic indications for transplant. J Heart Lung Transplant 2016;35:1170–84. https://doi.org/10.1016/j.healun.2016.09.001.
[18] Black CK, Termanini KM, Aguirre O, Hawksworth JS, Sosin M. Solid organ transplantation in the 21st century. Ann Transl Med 2018;6:409. https://doi.org/10.21037/atm.2018.09.68.
[19] Chapman JR, Webster AC, Wong G. Cancer in the transplant recipient. Cold Spring Harb Perspect Med 2013;3:a015677. https://doi.org/10.1101/cshperspect.a015677.
[20] Al-Adra DP, Hammel L, Roberts J, Woodle ES, Levine D, Mandelbrot D, et al. Pretransplant solid organ malignancy and organ transplant candidacy: a consensus expert opinion statement. Am J Transplant 2021;21:460–74. https://doi.org/10.1111/ajt.16318.
[21] Machuca TN, Keshavjee S. Transplantation for lung cancer. Curr Opin Organ Transplant 2012;17:479–84. https://doi.org/10.1097/MOT.0b013e328357fff6.
[22] Cai J. Double- and single-lung transplantation: an analysis of twenty years of OPTN/UNOS registry data. Clin Transpl 2007:1–8.
[23] Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Dobbels F, et al. The registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report-2012. J Heart Lung Transplant 2012;31:1073–86. https://doi.org/10.1016/j.healun.2012.08.004.
[24] Gottlieb J, Greer M, Sommerwerck U, Deuse T, Witt C, Schramm R, et al. Introduction of the lung allocation score in Germany. Am J Transplant 2014;14:1318–27. https://doi.org/10.1111/ajt.12752.
[25] Verleden GM, Fisher AJ. Lung transplantation and lung cancer: is there a link? Respiration 2011;81:441–5. https://doi.org/10.1159/000326934.
[26] Picard C, Grenet D, Copie-Bergman C, Martin N, Longchampt E, Zemoura L, et al. Small-cell lung carcinoma of recipient origin after bilateral lung transplantation for cystic fibrosis. J Heart Lung Transplant 2006;25:981–4. https://doi.org/10.1016/j.healun.2006.04.010.
[27] Trulock EP, Christie JD, Edwards LB, Boucek MM, Aurora P, Taylor DO, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fourth official adult lung and heart-lung transplantation report-2007. J Heart Lung Transplant 2007;26:782–95. https://doi.org/10.1016/j.healun.2007.06.003.
[28] Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dobbels F, Kirk R, et al. The Registry of the International Society for Heart and Lung Transplantation: Twenty-eighth Adult Lung and Heart-Lung Transplant Report–2011. J Heart Lung Transplant 2011;30:1104–22. https://doi.org/10.1016/j.healun.2011.08.004.
[29] Van Raemdonck D, Vos R, Yserbyt J, Decaluwe H, De Leyn P, Verleden GM. Lung cancer: a rare indication for, but frequent complication after lung transplantation. J Thorac Dis 2016;8:S915–24. https://doi.org/10.21037/jtd.2016.11.05.
[30] Du L, Pennell NA, Elson P, Hashemi-Sadraei N. Lung cancer treatment outcomes in recipients of lung transplant. Transl Lung Cancer Res 2015;4:784–91. https://doi.org/10.3978/j.issn.2218-6751.2015.12.08.
[31] Lee J, Kim HS, Lee CY, Chung LI, Yang WJ, Yu J, et al. Inverse Association of Post-transplant Malignancy and Graft Failure on Survival Outcome Following Double Lung Transplantation. 2023.
[32] Patterson GA, Cooper JD, Goldman B, Weisel RD, Pearson FG, Waters PF, et al. Technique of successful clinical double-lung transplantation. Ann Thorac Surg 1988;45:626–33. https://doi.org/10.1016/s0003-4975(10)64763-7.
[33] Yusen RD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Goldfarb SB, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-second Official Adult Lung and Heart-Lung Transplantation Report–2015; Focus Theme: Early Graft Failure. J Heart Lung Transplant 2015;34:1264–77. https://doi.org/10.1016/j.healun.2015.08.014.

[34] Zorn GL, McGiffin DC, Young KR, Alexander CB, Weill D, Kirklin JK. Pulmonary transplantation for advanced bronchioloalveolar carcinoma. J Thorac Cardiovasc Surg 2003;125:45–8. https://doi.org/10.1067/mtc.2003.72.
[35] Wang Y, Wei D, Wang Z, Zheng M, Chen J. Bilateral lung transplant for bronchioloalveolar carcinoma: first case in China. Exp Clin Transplant 2012;10:519–21. https://doi.org/10.6002/ect.2011.0186.
[36] Zhang-Velten ER, Gerber DE, Westover KD. Thirteen-year survival in a patient with diffuse bilateral Lepidic-predominant adenocarcinoma: a case report of lung transplantation and local salvage. JTO Clin Res Rep 2020;1:100094. https://doi.org/10.1016/j.jtocrr.2020.100094.
[37] Glanville AR, Wilson BE. Lung transplantation for non-small cell lung cancer and multifocal bronchioalveolar cell carcinoma. Lancet Oncol 2018;19:e351–8. https://doi.org/10.1016/S1470-2045(18)30297-3.
[38] Arenberg D, American College of Chest Physicians. Bronchioloalveolar lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132. https://doi.org/10.1378/chest.07-1383. 306S–13S.
[39] Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, et al. A consensus document for the selection of lung transplant candidates: 2014–an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2015;34:1–15. https://doi.org/10.1016/j.healun.2014.06.014.
[40] Leard LE, Holm AM, Valapour M, Glanville AR, Attawar S, Aversa M, et al. Consensus document for the selection of lung transplant candidates: an update from the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2021;40:1349–79. https://doi.org/10.1016/j.healun.2021.07.005.
[41] Cha YJ, Shim HS. Biology of invasive mucinous adenocarcinoma of the lung. Transl Lung Cancer Res 2017;6:508–12. https://doi.org/10.21037/tlcr.2017.06.10.
[42] Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6:244–85. https://doi.org/10.1097/JTO.0b013e318206a221.
[43] Fujikawa R, Muraoka Y, Kashima J, Yoshida Y, Ito K, Watanabe H, et al. Clinicopathologic and genotypic features of lung adenocarcinoma characterized by the International Association for the Study of Lung Cancer grading system. J Thorac Oncol 2022;17:700–7. https://doi.org/10.1016/j.jtho.2022.02.005.
[44] Lee MA, Kang J, Lee HY, Kim W, Shon I, Hwang NY, et al. Spread through air spaces (STAS) in invasive mucinous adenocarcinoma of the lung: incidence, prognostic impact, and prediction based on clinicoradiologic factors. Thorac Cancer 2020;11:3145–54. https://doi.org/10.1111/1759-7714.13632.
[45] Casali C, Rossi G, Marchioni A, Sartori G, Maselli F, Longo L, et al. A single institution-based retrospective study of surgically treated bronchioloalveolar adenocarcinoma of the lung: clinicopathologic analysis, molecular features, and possible pitfalls in routine practice. J Thorac Oncol 2010;5:830–6. https://doi.org/10.1097/jto.0b013e3181d60ff5.
[46] Lee KS, Kim Y, Han J, Ko EJ, Park CK, Primack SL. Bronchioloalveolar carcinoma: clinical, histopathologic, and radiologic findings. Radiographics 1997;17:1345–57. https://doi.org/10.1148/radiographics.17.6.9397450.
[47] Yoshizawa A, Motoi N, Riely GJ, Sima CS, Gerald WL, Kris MG, et al. Impact of proposed IASLC/ATS/ERS classification of lung adenocarcinoma: prognostic subgroups and implications for further revision of staging based on analysis of 514 stage I cases. Mod Pathol 2011;24:653–64. https://doi.org/10.1038/modpathol.2010.232.
[48] Russell PA, Wainer Z, Wright GM, Daniels M, Conron M, Williams RA. Does lung adenocarcinoma subtype predict patient survival?: a clinicopathologic study based on the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary lung adenocarcinoma classification. J Thorac Oncol 2011;6:1496–504. https://doi.org/10.1097/JTO.0b013e318221f701.
[49] Warth A, Muley T, Meister M, Stenzinger A, Thomas M, Schirmacher P, et al. The novel histologic International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification system of lung adenocarcinoma is a stage-independent predictor of survival. J Clin Oncol 2012;30:1438–46. https://doi.org/10.1200/JCO.2011.37.2185.
[50] Horiguchi T, Yanagi S, Tomita M, Maeda R, Uto K, Shigekusa T, et al. A case of bilateral invasive mucinous adenocarcinoma of the lung with severe productive cough and dyspnea successfully treated with palliative lung lobectomy. Respir Med Case Rep 2021;32:101368. https://doi.org/10.1016/j.rmcr.2021.101368.
[51] Matsui T, Sakakura N, Koyama S, Nakanishi K, Sasaki E, Kato S, et al. Comparison of surgical outcomes between invasive mucinous and non-mucinous lung adenocarcinoma. Ann Thorac Surg 2021;112:1118–26. https://doi.org/10.1016/j.athoracsur.2020.09.042.
[52] Lee HY, Cha MJ, Lee KS, Lee HY, Kwon OJ, Choi JY, et al. Prognosis in resected invasive mucinous adenocarcinomas of the lung: related factors and comparison with resected nonmucinous adenocarcinomas. J Thorac Oncol 2016;11:1064–73. https://doi.org/10.1016/j.jtho.2016.03.011.
[53] Xu X, Shen W, Wang D, Li N, Huang Z, Sheng J, et al. Clinical features and prognosis of resectable pulmonary primary invasive mucinous adenocarcinoma. Transl Lung Cancer Res 2022;11:420–31. https://doi.org/10.21037/tlcr-22-190.
[54] Cha YJ, Kim HR, Lee H-J, Cho BC, Shim HS. Clinical course of stage IV invasive mucinous adenocarcinoma of the lung. Lung Cancer 2016;102:82–8. https://doi.org/10.1016/j.lungcan.2016.11.004.
[55] Chen Z, Li M, Ma K, Shang G, Liang J, Yin J, et al. Analysis of the clinicopathological characteristics, genetic phenotypes, and prognostic of pure mucinous adenocarcinoma. Cancer Med 2020;9:517–29. https://doi.org/10.1002/cam4.2726.
[56] Qu Y, Zhao D, Mu J, Che N, Zhang C, Liu Z, et al. Prognostic analysis of primary mucin-producing adenocarcinoma of the lung: a comprehensive retrospective study. Tumour Biol 2016;37:887–96. https://doi.org/10.1007/s13277-015-3869-1.
[57] Lakshmanan I, Ponnusamy MP, Macha MA, Haridas D, Majhi PD, Kaur S, et al. Mucins in lung cancer: diagnostic, prognostic, and therapeutic implications. J Thorac Oncol 2015;10:19–27. https://doi.org/10.1097/JTO.0000000000000404.
[58] Rajeev LK, Thottian AGF, Amirtham U, Lokanatha D, Jacob LA, Babu MCS, et al. Primary mucinous carcinomas of the lung: clinical characteristics and treatment outcomes. Lung India 2020;37:491–4. https://doi.org/10.4103/lungindia.lungindia_52_20.
[59] Dickson RP, Davis RD, Rea JB, Palmer SM. High frequency of bronchogenic carcinoma after single-lung transplantation. J Heart Lung Transplant 2006;25:1297–301. https://doi.org/10.1016/j.healun.2006.09.009.
[60] Subramanian MP, Meyers BF. Bilateral versus single lung transplantation: are two lungs better than one? J Thorac Dis 2018;10:4588–601. https://doi.org/10.21037/jtd.2018.06.56.
[61] Kotsimbos T, Williams TJ, Anderson GP. Update on lung transplantation: programmes, patients and prospects. Eur Respir Rev 2012;21:271–305. https://doi.org/10.1183/09059180.00006312.
[62] Geltner C, Jamnig H, Bucher B. Lung transplantation for Bronchiolo-alveolar lung carcinoma. Lung Cancer 2002;37:S27.
[63] Szeto WY, Kreisel D, Karakousis GC, Pochettino A, Sterman DH, Kotloff RM, et al. Cardiopulmonary bypass for bilateral sequential lung transplantation in patients with chronic obstructive pulmonary disease without adverse effect on lung function or clinical outcome. J Thorac Cardiovasc Surg 2002;124:241–9. https://doi.org/10.1067/mtc.2002.121303.
[64] Triantafillou AN, Pasque MK, Huddleston CB, Pond CG, Cerza RF, Forstot RM, et al. Predictors, frequency, and indications for cardiopulmonary bypass during lung transplantation in adults. Ann Thorac Surg 1994;57:1248–51. https://doi.org/10.1016/0003-4975(94)91367-6.
[65] Hlozek CC, Smedira NG, Kirby TJ, Patel AN, Perl M. Cardiopulmonary bypass (CPB) for lung transplantation. Perfusion 1997;12:107–12. https://doi.org/10.1177/026765919701200205.
[66] Gammie JS, Cheul Lee J, Pham SM, Keenan RJ, Weyant RJ, Hattler BG, et al. Cardiopulmonary bypass is associated with early allograft dysfunction but not death after double-lung transplantation. J Thorac Cardiovasc Surg 1998;115:990–7. https://doi.org/10.1016/s0022-5223(98)70396-4.
[67] Aeba R, Griffith BP, Kormos RL, Armitage JM, Gasior TA, Fuhrman CR, et al. Effect of cardiopulmonary bypass on early graft dysfunction in clinical lung transplantation. Ann Thorac Surg 1994;57:715–22. https://doi.org/10.1016/0003-4975(94)90573-8.
[68] Zheng X-M, Yang Z, Yang G-L, Huang Y, Peng J-R, Wu M-J. Lung injury after cardiopulmonary bypass: alternative treatment prospects. World J Clin Cases 2022;10:753–61. https://doi.org/10.12998/wjcc.v10.i3.753.
[69] Murphy GJ, Angelini GD. Side effects of cardiopulmonary bypass: what is the reality? J Card Surg 2004;19:481–8. https://doi.org/10.1111/j.0886-0440.2004.04101.x.
[70] Gómez-Román JJ, Del Valle CE, Zarrabeitia MT, Martínez JC, Goñi FZ, Lera RM, et al. Recurrence of bronchioloalveolar carcinoma in donor lung after lung transplantation: microsatellite analysis demonstrates a recipient origin. Pathol Int 2005;55:580–4. https://doi.org/10.1111/j.1440-1827.2005.01872.x.
[71] Bittner HB, Binner C, Lehmann S, Kuntze T, Rastan A, Mohr FW. Replacing cardiopulmonary bypass with extracorporeal membrane oxygenation in lung transplantation operations. Eur J Cardiothorac Surg 2007;31. https://doi.org/10.1016/j.ejcts.2006.11.050. 462–7; discussion 467.
[72] Hoetzenecker K, Benazzo A, Stork T, Sinn K, Schwarz S, Schweiger T, et al. Bilateral lung transplantation on intraoperative extracorporeal membrane oxygenator: an observational study. J Thorac Cardiovasc Surg 2020;160:320–327.e1. https://doi.org/10.1016/j.jtcvs.2019.10.155.
[73] Biscotti M, Yang J, Sonett J, Bacchetta M. Comparison of extracorporeal membrane oxygenation versus cardiopulmonary bypass for lung transplantation. J Thorac Cardiovasc Surg 2014;148:2410–5. https://doi.org/10.1016/j.jtcvs.2014.07.061.
[74] Fessler J, Sage E, Roux A, Feliot E, Gayat E, Pirracchio R, et al. Is extracorporeal membrane oxygenation withdrawal a safe option after double-lung transplantation? Ann Thorac Surg 2020;110:1167–74. https://doi.org/10.1016/j.athoracsur.2020.03.077.
[75] Świtlik WZ, Szemraj J. Circulating miRNAs as non-invasive biomarkers for non-small cell lung cancer diagnosis, prognosis and prediction of treatment response. Postepy Hig Med Dosw (Online) 2017;71:649–62. https://doi.org/10.5604/01.3001.0010.3845.
[76] Farooq M, Herman JG. Noninvasive diagnostics for early detection of lung Cancer: challenges and potential with a focus on changes in DNA methylation. Cancer Epidemiol Biomark Prev 2020;29:2416–22. https://doi.org/10.1158/1055-9965.EPI-20-0704.
[77] Ulivi P, Zoli W. miRNAs as non-invasive biomarkers for lung cancer diagnosis. Molecules 2014;19:8220–37. https://doi.org/10.3390/molecules19068220.
[78] Soo J, Schroers-Martin J, Garofalo A, Kurtz D, D'Emilio N, Luikart H, et al. Early detection of post-transplant lymphoproliferative disorder using circulating tumor DNA. J Heart Lung Transplant 2019;38:S12–3.
[79] Chen K, Zhao H, Shi Y, Yang F, Wang LT, Kang G, et al. Perioperative Dynamic changes in circulating tumor DNA in patients with lung Cancer (DYNAMIC). Clin Cancer Res 2019;25:7058–67. https://doi.org/10.1158/1078-0432.CCR-19-1213.
[80] Kaiser LR, Pasque MK, Trulock EP, Low DE, Dresler CM, Cooper JD. Bilateral sequential lung transplantation: the procedure of choice for double-lung

replacement. Ann Thorac Surg 1991;52. https://doi.org/10.1016/0003-4975(91)90903-4. 438–45; discussion 445–446.

[81] Bonnette P, Bisson A, Ben el Kadi N, Colchen A, Leroy M, Caubarrère I, et al. Double lung transplantation. The "bilateral single" graft. Presse Med 1991;20:2058–60.

[82] Boasquevisque CHR, Yildirim E, Waddel TK, Keshavjee S. Surgical techniques: lung transplant and lung volume reduction. Proc Am Thorac Soc 2009;6:66–78. https://doi.org/10.1513/pats.200808-083GO.