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REVIEW

OPTIMAL MANAGEMENT OF LONG-TERM AIR LEAKAGE AFTER LUNG RESECTIONS FOR CANCER

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ABSTRACT

Lung resection is the main diagnostic and therapeutic surgical intervention in terms of lung cancer management. Air leak through pleural drains often occurs after lung resections due to damage to the pulmonary parenchyma. Therefore, proper drainage of the pleural cavity is very important for the successful outcome of the operation. The installation of a single pleural drainage after anatomical resection, the refusal to use vacuum aspiration and the earliest possible removal of drains contribute to the rapid activation of patients in the postoperative period. Prolonged air leakage (PAL) after lung resection, on average, develops in 15 % of lung cancer patients, remaining one of the most common complications adversely affecting the rehabilitation of patients and leading to delayed discharge from the hospital. The incidence of empyema with prolonged air leakage is 10.4 % with air discharge for more than 7 days compared to 1 % with air leaks less than or equal to 7 days. PAL requires prolonged drainage of the pleural cavity, which increases postoperative pain, causing shallow breathing, difficulty coughing leads to an increased risk of pneumonia, decreased mobility is accompanied by a high risk of thromboembolic complications. In addition, the treatment of complications is associated with the need to perform additional invasive interventions such as chemical or mechanical pleurodesis. Prolonged air leakage is associated with an increase in hospital mortality. Patients with an air leak have a 3.4 times greater risk of death than patients without it. Active tactics in relation to PAL include preoperative prediction of a high risk of complications, intraoperative measures to prevent air leak from the lung parenchyma and postoperative treatment to reduce the duration of PAL. The urgency of the problem is due to the fact that prolonged air leakage in patients with lung cancer after organ-preserving operations is associated with an increased risk of infectious complications due to the need for prolonged drainage of the pleural cavity. In this review, the main attention is paid to two components of postoperative management of PAL: diagnosis with an accurate assessment of the intensity of air leak and treatment of alveolar-pleural fistulas.

Keywords:
lung resection, prolonged air leakage, chest tube management, digital drainage systems, autologous blood patch pleurodesis, outpatient management

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ОБЗОР

ОПТИМАЛЬНОЕ ЛЕЧЕНИЕ ДЛИТЕЛЬНОЙ УТЕЧКИ ВОЗДУХА ПОСЛЕ РЕЗЕКЦИЙ ЛЕГКОГО ПО ПОВОДУ РАКА

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РЕЗЮМЕ

Резекция легкого – основное диагностическое и лечебное хирургическое вмешательство при раке легкого. Сброс воздуха по плевральным дренажам нередко возникает после операций на легких из-за повреждения легочной паренхимы. Следовательно, правильное дренирование плевральной полости имеет весьма важное значение для успешного исхода операции. Установка единственного плеврального дренажа после анатомической резекции, отказ от применения вакуум-аспирации и максимально раннее удаление дренажей способствуют быстрой активизации больных в послеоперационном периоде. Длительная утечка воздуха (ДУВ) после резекции легкого в среднем, развивается у 15 % больных раком легкого, оставаясь одним из наиболее распространенных осложнений, неблагоприятно влияющим на реабилитацию больных и приводящим к задержке выписки из больницы. Частота развития эмпиемы при ДУВ составляет 10,4 % при сбросе воздуха более 7 дней по сравнению с 1 % при утечках воздуха менее или равных 7 дням. ДУВ требует длительного дренирования плевральной полости, что усиливает послеоперационную боль, вызывая поверхностное дыхание, затрудненное откашливание приводит к повышенному риску развития пневмонии, снижение подвижности сопровождается высоким риском тромбоэмболических осложнений. Кроме того, лечение осложнения связано с необходимостью выполнения дополнительных инвазивных вмешательств таких как химический или механический плевродез. Длительная утечка воздуха связана с увеличением госпитальной летальности. Пациенты с утечкой воздуха имеют в 3,4 раза больший риск смерти, чем больные без нее. Активная тактика применительно к ДУВ включает в себя предоперационное прогнозирование высокого риска осложнения, интраоперационные мероприятия для предотвращения сброса воздуха из паренхимы легкого и послеоперационное лечение для сокращения продолжительности ДУВ. Актуальность проблемы обусловлена тем, что длительная утечка воздуха у больных раком лёгкого после органосохранных операций связана с повышением риска развития инфекционных осложнений в связи с необходимостью длительного дренирования плевральной полости. В данном обзоре основное внимание уделено двум составляющим послеоперационного ведения ДУВ: диагностике с точной оценкой интенсивности сброса воздуха и лечению альвеолярно-плевральных свищей.

Ключевые слова:
резекция легких, длительная утечка воздуха, ведение плевральных дренажей, цифровые дренажные системы, плевродез аутологичной кровью, амбулаторное ведение

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INTRODUCTION

Lung resection remains the main diagnostic or therapeutic intervention in thoracic surgery. In addition to a comprehensive preoperative examination, careful surgical intervention, proper postoperative care is absolutely necessary to achieve a favorable result of surgical treatment of lung cancer (LC). Air discharge through pleural drains often occurs after lung operations due to damage to the pulmonary parenchyma. The frequency of air discharge after lung resection ranges from 25 % to 50 % on the 1st day after surgery and up to 20 % on the 2nd day [1; 2]. Therefore, proper drainage of the pleural cavity is very important for the successful outcome of the operation. The installation of a single pleural drainage (PD) after anatomical resection, the refusal to use vacuum aspiration and the earliest possible removal of drainage against the background of sufficient anesthesia contribute to the rapid activation and rehabilitation of patients in the postoperative period. Air discharge in most cases stops spontaneously, but when it continues for 5–7 days after surgery, such a prolonged air leak (PAL) is considered a complication [3]. PAL due to the communication of the alveoli of the pulmonary parenchyma distal to the segmental bronchus with the pleural cavity [3] after lung resection, on average, develops in 15 % of patients with RL, remaining one of the most common complications adversely affecting the rehabilitation of patients and leading to delayed discharge from the hospital [4].

Improved Postoperative Rehabilitation (ERAS) programs are designed in such a way as to counteract possible complications with a scientifically based approach to their prevention and treatment. Active tactics in relation to PAL include preoperative prediction of a high risk of complications, intraoperative measures to prevent air discharge from the lung parenchyma and postoperative treatment to reduce the duration of PAL. In this review, the main attention is paid to two components of postoperative management of PAL: diagnosis with an accurate assessment of the intensity of air discharge and treatment of alveolar-pleural fistulas.

Number of pleural cavity drains

After anatomical resection of the lungs, an apical drainage tube for air removal and a basal drainage tube for fluid removal are traditionally installed. The need for a traditional approach has recently been challenged in the literature. To date, 4 randomized clinical studies (RCSs) have been conducted [5–8], one non-randomized study [9] and two meta-analyses [10; 11] that examined the results of postoperative management of pleural drainage after anatomical lung resections. They report on the duration of standing PD, the duration of hospital stay (DHS), the severity of postoperative pain and complications. No study provides data on the advantage of two PD compared to one pleural drainage. A shorter duration of standing PD and DHSwas found in one RCS [6] and in both meta-analyses [10; 11]. One meta-analysis [10] and 3 clinical studies [5; 7; 9] indicate a decrease in postoperative pain. Study of postoperative complications in 3 RCSs [5–7] and in both meta-analyses [12; 13] revealed no differences depending on the amount of PD, as well as in the need for repeated drainage of the pleural cavity.

It turns out that one drainage of the pleural cavity is quite enough, and the combined data indicate that one PD reduces the duration of standing PD and DHS. In fact, in patients with PAL and clinical manifestations of pneumothorax that are not controlled by a single PD, it may be necessary to install a second drainage. It is important that according to the literature data, there was no decrease in the need for repeated drainage of the pleural cavity when installing two drains [5–7; 10; 11]. ERAS protocols indicate the successful use of a single PD to control air discharge after lung resection [14]. Therefore, despite the traditional use of two drains, one signal drainage of the pleural cavity is quite sufficient to control air discharge and manage patients with advanced PAL.

Assessment of air discharge intensity

Traditional analog systems allow only a subjective static assessment of air discharge by PD. Digital devices provide more objective data on the intensity of air discharge by measuring and continuously recording the values of the air flow in the form of volume per unit of time, i.e. ml/min. The role of chest radiography has also been recently revised. In addition, patients are often discharged with portable drainage devices and, therefore, need to be assessed on an outpatient basis [12]. It is important to note that the methods discussed below are limited only to the discharge of air from the alveolar-pleural, but not the bronchopleural fistula, which always requires a different treatment tactic.

The initial pleural drainage systems (IPDS) were three-balloon drainage devices. The most common analog drainage devices used today are the well-known: Pleur-evac® (Teleflex Incorporated, USA) and Atrium® (Maquet Getinge Group, Germany) [12]. The devices consist of a liquid collection chamber and a water gate chamber for measuring the intensity of air discharge. Air discharge is measured by the formation of air bubbles in the water gate chamber. The assessment of air discharge is made by registering a number on a numbered column into which air bubbles fall when the patient coughs or exhales; the higher the number reached, the greater the intensity of air discharge. Attempts to quantify the intensity of air discharge have been made in several classifications. However, the Robert David Cerfolio Classification System, represented by 4 classes of air discharge, remains the most frequently cited: 1st degree when coughing, 2nd degree when exhaling, 3rd degree when inhaling and 4th degree with constant discharge (bubbling) during inhalation and exhalation [13]. Observation of air bubbles in the water gate chamber is a very subjective method, creating uncertainty about the presence or absence of a small air discharge, which makes provocative overlap of the PD permissible [15]. Provocative overlaps of PD delay the discharge of patients with no PAL or carry the risk of developing pneumothorax and subcutaneous emphysema in patients with PAL.

Since 2007, digital SDPS have become popular, which contribute to reducing variability in the assessment of the intensity of air discharge when making clinical decisions and timely diagnosis of PAL. They allow you to accurately measure intrapleural pressure and maintain its stable negative parameters using an electronic sensor and a digital console. In addition, digital IPDSs are more portable compared to water-gate IPDSs, which facilitates physical activity of patients [12].

It was expected that the protocols developed on the basis of the use of digital IPDS would lead to simpler postoperative management of pleural drainage. Objective measurement of the intensity of air discharge will allow medical personnel to determine in time when the air leak has stopped, which should facilitate the earliest possible removal of PD and discharge from the hospital. On the other hand, it was assumed that the use of digital IPDS would ensure the active identification of patients with the development of PAL. Identification of PAL will help to determine in a timely manner the optimal management tactics for such patients and those who can be discharged from the hospital with portable drainage devices.

Currently, Thopaz® (Medela Healthcare, Baar, Switzerland) and Atmos® (Medizin Technik, Germany) are available to measure the intensity of air discharge, which allow continuous measurement of air flow and record it as a graph for 12–48 hours [15]. The potential advantages of more objective measurements provided by digital SDPS are considered to be: the possibility of the earliest possible removal of PD, fewer attempts of provocative squeezes and early prediction or early diagnosis of PAL [12]. Numerous RCSs have been carried out comparing the effectiveness of digital and analog IPDS with the primary endpoint in the form of the duration of hospital stay and the duration of standing PD (Table 1).

The advantage of digital SDPS in terms of reducing the duration of standing PD and reducing DHShas been demonstrated in 5 studies [16–20]. One study showed a shorter duration of standing PD without a significant difference in DHS [21]. The absence of significant differences in the duration of standing PD and in DHSwas registered in four studies [1; 22; 23] (Table 1). Two randomized studies showed that digital devices led to fewer provocative pinching PD [1; 22].

Possible explanations for such different results are the lack of consensus on the intensity of air discharge before the removal of PD and different amounts of PD. In fact, the intensity of the air flow used as a threshold value before removing drains from the pleural cavity ranges from 0 to 40 ml/min during various time intervals from 8 to 12 hours [20–24]. In addition to air discharge, the amount of liquid separated by PD is another criterion that is usually taken into account before removing drains. There is also no consensus regarding the amount of liquid allowed for the removal of PD with fluctuations in volume from 200 to 450 ml in 24 hours [21–24]. In addition, PD is not necessarily removed immediately after the cessation of air discharge, but usually during the day after the morning round. Thus, as soon as the final criteria are established, continuous monitoring of air discharge by digital drainage devices will finally make it possible to really benefit from the timely removal of PD.

The first meta-analysis concerning the use of various SDPS after lung resection was undertaken by S. Coughlin et al. in 2012. It analyzes 4 RCSs conducted during the period from 2001 to 2007 [16–19]. There were no significant differences in terms of the duration of air discharge, the frequency of blowing, the duration of standing PD and the duration of hospital stay when comparing the use of IPDS with vacuum aspiration or with a water gate [25]. In 2018, J. Zhou and colleagues conducted a meta-analysis of 10 RCSs involving 1601 patients on the same issues and in the same comparison groups. As a result, based on the results of their meta-analysis, the role of a water-gate or vacuum-aspiration IPDS still remained unclear. Nevertheless, the need for selective application of vacuum aspiration was justified by the presence of residual or increasing pneumothorax [26]. Recently, the use of digital IPDS after lung resections has become more and more popular. J. Zhou et al. in 2018 and N. Wang et al. in 2019. They spoke in favor of the clinical use of digital IPDS in patients who underwent lung resection to reduce the time of air discharge, the duration of standing PD, the duration of hospital stay compared with aspiration IPDS [26].

The last systematic review revealed 21 comparative RCSs of the effectiveness of digital and analog IPDS with the participation of 3399 patients, men

Table 1. Results of 10 RCSs comparing the effectiveness of digital and analog pleural drainage systems

Author/year	N/M (%)/ Ave. Age	Approach	Surgery type	Complications (%)	DHS
Cerfolio R. J., Bryant A. 2008 [20]	100/51 %/ 62.0	VATS: 0 % Thoracotomy: 100 %	LE: 55 % SE: 16 % AR: 29 %	No data	3.3 vs. 4.0 Days (*p* = 0.055)
Filosso P. L. et al. 2010 [22]	31/67.7 %/ 69.6 ± 3.4	VATS: 0 % Thoracotomy: 100 %	LE: 100 %	No data	8 vs. 7 Days (*p* = 0.0385)
Brunelli A. et al. 2010 [21]	166/72.9 %/ 66.7 ± 10.9	VATS: 0 % Thoracotomy: 100 %	LE: 100 %	15,06 %	6.4 vs. 6.3 Days ($p < 0.05$)
Bertolaccini L. et al. 2011 [24]	100/59 %/ 65.5 ± 13.6	No data	LE: 48 % SE: 6 % AR: 46 %	2 %	6.5 vs.7.1 Days (*p* = 0.09)
Pompili C. et al. 2014 [23]	390/52.3 %/ 66.2	VATS: 80.84 % Thoracotomy: 19.16 %	LE: 85.3 % SE: 14.7 %	No data	4.6 vs. 5.6 Days ($p < 0.0001$)
Lijkendijk M. et al. 2015 [27]	105/37.1 %/ 68.3	VATS: 39.04 % Thoracotomy: 60.96 %	LE: 100 %	No data	4 vs. 5 Says (*p* = 0.65)
Gilbert S. et al. 2015 [1]	176/36.3 %/ 68.0	VATS: 72.09 % Thoracotomy: 27.91 %	LE: 76.74 % SE: 23.26 %	13,64 %	4.0 vs. 4.0 Days (*p* = 0.09)
Lococo F. et al. 2017 [29]	95/51.5 %/ 63.6 ±13.0	No data	LE: 52.63 % AR: 47.37 %	2,11 %	5.8 vs. 6.2 Days (*p* = 0.5)
Plourde M. et al. 2018 [28]	215/43.2 %/ 67.5 ± 9.3	VATS: 83.72 % Thoracotomy: 16.28 %	LE: 93.49 % SE: 4.19 % AR: 2.32 %	5,12 %	4 vs. 5 Days (*p* = 0.47)

Note: N – number of patients; M (%) – male sex in %; VATS – video–assisted thoracoscopic surgery; LE – lobectomy; SE – segmntectomy; AR – atypical resection; DHS- duration of hospital stay.

make up 58.9 %, the average age of the subjects is 63.2 years, which were included in the meta-analysis [27]. The meta-analysis aimed to compare the clinical efficacy of digital and aspiration SDPS with a drainage device with a water gate in terms of their effect on the duration of standing PD, the frequency of PAL after lung resection and DHS. Data on surgical access were obtained in 2326 patients: 1439 (61.87 %) patients underwent thoracotomy and 887 (38.13 %) underwent video–assisted thoracoscopic surgery (VATS). The type of surgical intervention was established in 2744 patients: 2089 (76.13 %) underwent lobectomy or bilobectomy, 189 (6.89 %) – segmentectomy and 466 (16.98 %) – atypical resection or lung biopsy. Complications after lung resections, such as PAL, bleeding, atelectasis and pneumonia, are not uncommon, they account for about 6–23 %, 0.1–0.3 %, 1–20 % and 3–25 %, respectively. 9 RCSs selected for meta-analysis reported different rates of complications after lung resection in the range from 2 % to 61.54 % [12; 17; 19; 21–26].

13 studies [1; 16–20; 22–24; 28–31] with the participation of 1870 patients were analyzed to study the primary control point for which DHSwas selected. The use of digital IPDS or IPDS with a water gate was significantly associated with a shorter hospital stay than with the use of IPDS with vacuum aspiration; MD ranges between –1.40 (95 % CI: –2.20– –0.60) for digital IPDS and –1.05 (95 % CI: –1.91– –0.18) for IPDS with a water gate [27]. Regarding the duration of standing PD, 10 studies involving 2124 patients were analyzed [1; 17; 18; 20; 23; 24; 28–31]. Digital IPDS significantly reduced the duration of standing PD (MD: –0.68; 95 % CI: –1.32– –0.04), while the value of the IPDS with a water gate in reducing the duration of standing PD remained unconvincing. 14 studies have been studied on the problem of the occurrence of PAL, including data from 2,709 patients [17–21; 25; 28–31]. Despite the fact that digital and water–gate IPDS had a positive effect on the prevention of PAL, both methods did not achieve statistical significance (digital: OR = –0.76; 95 % CI: 0.42–1.39; water-gate: OR = 0.95; 95 % CI: 0.56–1.62) [27].

Meta-analysis showed that the use of both digital SDPS and a water gate is significantly associated with a shorter DHSthan when connecting PD to aspiration SDPS. Digital IPDS provided a reduction in the duration of standing PD by 0.68 days (MD: –0.68, 95 % CI: from –1.32 to –0.04), and a water gate by 0.45 days (MD: –0.45, 95 % CI: from –1.11 to 0.20) compared to the IPDS with vacuum aspiration. Digital SDPS led to a reduction in DHSby 1.4 days (MD: –1.40, 95 % CI: –2.20 to –0.60), while the use of a water gate is associated with a reduction in DHS-by 1.05 days (MD: –1.05, 95 % CI: –1.91 to –0.18) compared with aspiration SDPS [27]. It is logical that earlier removal of PD leads to a shorter stay in the hospital, which is the main result confirmed by meta-analysis.

The difference in results between the hospital stay and the duration of standing PD is explained: firstly, by the heterogeneity of the analyzed studies presented by different clinics and surgeons with their own experience; secondly, by the fact that the studies were conducted at different times for almost 20 years and, consequently, the results could be influenced by innovations in the field of anesthesiology and thoracic surgery.

As for PAL after lung resections, the use of digital IPDS had a positive, although not statistically reliable, effect on their frequency (OR = 0.76; CI: 0.42–1.39; p = 0.78). IPDS with a water gate also has a lower odds ratio OR (OR = 0.95; 95 % CI: 0.56–1.62) in the prevention of PAL in comparison with a vacuum-aspirated IPDS [27]. The results obtained are consistent with the recommendations for accelerated rehabilitation after lung surgery published in 2019 [32]. Routine use of vacuum aspiration for PD management after lung resection in the postoperative period is no longer recommended.

Thus, despite the absolute importance of drainage of the pleural cavity, PD causes pain, worsens lung function and prevents patients from performing physical exercises regardless of the surgical approaches used [33]. The inconveniences created by prolonged standing PD delay the postoperative rehabilitation of patients. Therefore, early removal of PD is essentially the ultimate goal of optimizing postoperative management after lung resection, allowing to reduce DHSand the costs associated with treatment [33].

In the postoperative period, chest radiography is usually prescribed, which, despite the minimal side effect, causes discomfort in patients, especially in the first days after surgery [1; 34]. In addition, it is now known that asymptomatic pneumothorax is safe and ERAS protocols recommend standard PD management [12; 35].

A retrospective review of 1,550 radiographs and related prospectively collected clinical data in 176 patients showed that the results of the RGC did not change the management tactics of patients who did not have clinical symptoms such as shortness of breath, chest pain, tachycardia or decreased oxygen saturation [29]. Similarly, in a meta-analysis involving 3,649 patients, the appointment of RGC only for clinical indications reduced the number of radiographs per patient by 3.15 without increasing mortality, stay in the intensive care unit or DHS [36].

The RCS results discussed in detail above include parameters important for ERAS protocols, such as: the frequency of PAL, the duration of standing PD, DHSand the presence of residual pneumothorax after removal of drains from the pleural cavity. Obviously, it makes no sense to repeat, noting that two protocols aimed at standardizing the management of patients after lung resection established a PD management regime with their connection to active vacuum aspiration until the 1st day of the postoperative period, followed by a transition to a water shutter in the absence of contraindications [12; 35]. It seems at the moment that the tactics of PD management adopted in a particular center are probably more important than the ongoing debate about the benefits and harms of using active vacuum aspiration.

Despite the fact that modern literature generally focuses on the conservative treatment of PAL, including outpatient management for persistent air discharge and observation of pneumothorax detected in RGC [35], patients who do not tolerate PAL, as well as with the threat of postoperative pneumonia or pleural empyema, invasive measures are shown to eliminate the complication. Among other things, it is necessary to continue studying new and old methods of active resolution of PAL.

Pleurodesis

Pleurodesis is performed without surgery at the patient's bedside using a chemical substance or autologous blood. The use of both methods is reported in small cohort and RCSs. Literature sources indicate that autologous blood pleurodesis (PAC) appears to be a promising way to resolve PAL.

Many drugs, such as talc, silver nitrate, doxycycline, tetracycline, bleomycin and interferon, are injected into the pleural cavity in order to cause inflammation leading to the adhesive process. For the formation of pleural accretions, chemicals require a good apposition of the visceral and parietal pleura. An inflammatory reaction often causes pain, fever, shortness of breath and even acute respiratory distress syndrome (ARDS). The literature supporting the use of chemical pleurodesis in the postoperative period is limited [38]. However, a retrospective review of 41 patients after lung resection who received chemical pleurodesis using talc, doxycycline and a combination of these drugs revealed successful termination of PAL in 40 (97.6 %) patients. The average duration of PAL after administration of the sclerosing agent was 2.8 days. Pleural empyema developed in 1 (2.5 %) patient [39]. An interesting clinical study of the effectiveness of three methods of treatment of PAL after lung resection was published by S Jabłonski, in 2018. Chemical pleurodesis with an aqueous solution of iodine in 30 patients and intrapleural administration of 200 mg of doxycycline in 34 patients was compared with a control group of 35 patients who were administered only lidocaine solution. The shortest standing time of PD and DHSwas observed in the pleurodesis group with an aqueous solution of iodine ($p < 0.001$), which was associated with strongly noticeable chest pain ($p < 0.0001$) [39]. Despite the seemingly encouraging results, surgeons are reluctant to use chemical pleurodesis after lung resection, since talc, being essentially a foreign body, causes a rough adhesive process that makes repeated surgical intervention extremely difficult. Other methods of chemical pleurodesis with the introduction of other drugs are accompanied by severe pain and are not always effective.

On the contrary, PAK as a method of pleurodesis has been studied more thoroughly and is more often discussed in the timely literature. PAK was proposed 35 years ago for the treatment of patients with spontaneous pneumothorax. The first report on the use of PAK in patients with PAL after lobectomy was published 30 years ago. It refers to 2 patients who were successfully treated with PAK as a "last resort" of conservative therapy for PAL [40]. Several theories have tried to explain the mechanism of action; one hypothesis suggests that blood initiates an inflammatory reaction of the pleura, leading to an adhesive process, while another hypothesis supports the idea that the alveolar-pleural fistula is directly clogged with blood [41].

Since then, several studies have been conducted on this issue. The usefulness of ABP for the treatment of PAL has been the subject of two systematic reviews and meta-analysis [42]. The first review published by K. Manley and colleagues in 2012 included patients with PAL, which occurred both as a result of spontaneous pneumothorax and after lung resection. The second review, devoted to the study of the role of ABP, included 10 studies involving 198 patients who developed PAL after thoracic surgery [42].

Usually, 50 to 120 ml of blood is taken from the peripheral vein of the patient and injected into the pleural cavity through drainage. The timing of the procedure, depending on the day of the postoperative period in which the procedure was performed, is shown in Table 2. The amount of blood used for pleurodesis varied from 45 to 250 ml. In one study, patients were randomized for ABP with blood volumes of 50 or 100 ml and it was concluded that patients of the second group had a significantly shorter drainage time of the pleural cavity [43]. In 9 studies, blood was injected directly through pleural drainage, and in one study, an additional catheter was installed through pleural drainage to ensure more targeted blood injection [44]. Patients with a "residual space" confirmed by the results of chest radiography were included in two studies [45; 46], and in the third study, most patients had a "residual space" [47]. In 4 studies, it is reported that in some cases more than one blood injection was required [44, 46–48], so in one observation, four injections were reported in one patient table 2 [44]. ALK TKI in subsequent lines of targeted therapy of previously treated ALK-positive NSCLC.

In 3 studies, PAL was present for almost two weeks before the decision was made to proceed with PAK [44; 47]. In addition, in a number of studies before PAK, such measures as pleurodesis with the introduction of tetracycline or other methods of chemical pleurodesis were unsuccessfully used. Therefore, it is realistic to assume that the PAK has successfully eliminated PAL in patients with prolonged or very prolonged air discharge.

As for the treatment of PD after the PAK procedure, it is more often described lifting the drainage tube above the patient's level with the cessation of vacuum aspiration, in one study it was reported that vacuum aspiration continued when the drainage was raised, and in another one – the drainage was squeezed for 30 minutes, and then connected to a water gate. It is worth noting that in the last study, all patients had a second PD, which remained connected to the water gate without aspiration. Usually, ABP were performed without any additional blood treatment, in one study blood was mixed with Picibanil [45], and in another study a pneumoperitoneum was applied the day before ABP [46].

In 2 studies, complications after ABP were not reported [43; 48], in 2, one case of empyema was registered [44; 49]. In addition, a total of 17 patients had fever after PAK, but only two had a positive microbiological examination (Table 2). It is important to observe complete sterility, since blood is a known nutrient medium for bacteria [42].

As a result, meta-analysis showed that the success rate of ABP for resolving postoperative PAL within 48 hours was 83.7 % (95 % CI: 75.7–90.3) for all included patients and 85.7 % (95 % CI: 74.4–94.0) in patients who underwent lung resection. The total frequency of empyema after the procedure was 1.5 %, and the frequency of fever was 8.6 %. To identify a potential correlation between the amount of blood used for pleurodesis and the success of the ABP, the Pearson coefficient was calculated; no correlation could be detected ($r = 0.049$, $p = 0.893$) [42].

A relatively small study by J. J. Rivas de Andres et al. demonstrated the same level of success as the meta-analysis. At the same time, according to the results of the last RCS from Mayo Clinic, the resolution rate of PAL after PAK was 65 %, which contributed to a tendency to decrease the duration of standing PD from 16 to 11 days (HR = 1.5–2; $p = 0.14$,), DHS ($p = 0.13$) and a significant decrease in the number of repeated hospitalizations (HR = 0.16; $p = 0.02$), and repeated operations for PAL or empyema (HR = 0.11; $p = 0.05$) [48].

In general, the literature supports the opinion that PAK is an effective means of eliminating PAL in patients after lung resections. Taking into account the available evidence of efficacy and the low complication rate, ABP should be considered for the elimination of PAL within the framework of ERAS protocols [13]. In addition, it is interesting to conduct studies to compare ABP with the management of patients on portable drainage devices, taking into account the duration of standing PD and DHSas the main endpoints.

Endobronchial valves (EV)

EV are currently being implemented in the form of endobronchial valves (Zephyr®, PulmonX Inc.)

and intrabronchial valves (IBV/SVS system®, Spiration Inc.) [50]. EVimplantation is described in detail and is carried out in three stages: 1. Identification of segmental or sub-segmental bronchus leading to PAL by means of successive balloon inflations with monitoring of the termination of air discharge through the drainage of the pleural cavity; 2. selection of a suitable valve size according to the caliber provided by the manufacturer; 3 valve installation [51].

In the modern literature, special attention is not paid to the treatment of postoperative PAL using the installation of EC. Publications on their use for the treatment of PAL are limited to a series of cases that include postoperative PAL, along with other causes such as spontaneous, traumatic and iatrogenic pneumothorax [51]. An international study involving 40 patients who had EVinstalled to eliminate PAL included 8 patients with postoperative PAL. After the installation of EV in 19 (47.5 %) of 40 patients, PAL was completely eliminated, in 18 (45 %) patients the intensity of air discharge decreased, in 2 (5 %) there was no response. The median and average duration of pleural drainage after the procedure were 7.5 days and 21 days, respectively. The median and average DHSvalues after valve installation were 19 days and 11 days, respectively [52].

In another study, 9 patients with an average duration of PAL of more than 4 weeks were treated with the help of EC. Successful valve installation was performed in 7 (77.8 %) patients; 3.5 valves were used on average. The average duration of PAL after valve installation was 1 day and four patients were discharged within 2–3 days after valve installation [53]. In another study, 21 (10 after lung resection) patients with PAL underwent 24 procedures to install EC. Drainage of the pleural cavity lasted on average for 15 days, and the average DHS was 5 days after the valve was installed [54].

Obviously, the use of EVfor the treatment of postoperative PAL is limited to a small number of cases. Endobronchial valves were mainly used as a last resort or in patients with the inability to use other methods of treatment. Perhaps their earlier use can improve the results. To compare EV with the standard treatment of PAL, a multicenter prospective RCS (Valves Against Standard Therapy) is currently being conducted, which is not limited to postoperative PAL [55]. In addition to the risk of increased exacerbations of COPD, the development of pneumonia and hemoptysis, the installation of EVin postoperative PAL may be accompanied by the development of atelectasis. Therefore, until more data is obtained, EV should remain the last resort to eliminate postoperative PAL.

Repeated operation

There are no studies comparing repeat surgery with other PAL treatments. Many intraoperative methods of preventing PAL have been described, including: strengthening of mechanical suture lines, the use of surgical sealants, the creation of pleural awnings and

Table 2. Clinical studies of pleurodesis with autologous blood

Author/year	Patients number	Time of con-ducting the procedure	Volume of the infused fluid (ml)	Complictions
Yokomise H., et al.1998 [45]	10	8.7 ± 4.7	50	Fever 5
Droghetti A., et al. 2006 [47]	21	11 on average	50–150	Fever 1
Andreetti C., et al. 2007 [43]	25	6 on average	50 or 100	Absent
Oliveira FH., et al. 2010 [44]	27	10.6 on average	90	Empyema 1, Fever 1
Korasidis S., et al. 2010 [46]	39	No data	100	Fever 6
Dye K., et al. 2020 [49]	19	7 on average	45–120	Empyema 1
Hasan IS., et al. 2021 [48]	34	6 days	90	Absent

the imposition of pneumoperitoneum [12]. However, all of them have not been studied in conditions of repeated use.

However, repeated intervention is rarely required [56]. Probably, the operation is most indicated when intensive air discharge is unexpectedly detected during the first 24 hours after lung resection. Early repeated surgery helps to eliminate the failure of bronchial sutures, identify and suture damage to the lung parenchyma or strengthen the lines of the mechanical suture and apply the above-mentioned methods to prevent PAL. ERAS protocols for lung resection do not provide for repeated operations and are mainly focused on more conservative treatment of PAL [14]. Repeated surgery, as a rule, is not indicated for many patients and is performed in the early postoperative period with intensive PAL or in cases of delayed occurrence of massive air discharge.

Outpatient management

PAL, will develop independently of the best practice of thoracic surgery. Until the invasive methods of treatment of PAL are thoroughly studied to maximize the impact, ERAS protocols provide for outpatient management of PAL. Three positions should be clearly defined in the protocols: 1. when to connect a sick patient to a portable drainage device; 2. how and when to conduct outpatient monitoring; 3. what are the criteria for removing drainage from the pleural cavity.

R. J. Cerfolio et al. connected the Heimlich valve to PD in 55 patients with air discharge, of which 22 stopped during the day, but 33 patients were diagnosed with PAL. In 6 cases, the Heimlich valve had no effect, requiring the PD to be reconnected to the water valve or to the vacuum aspirator; in all patients, air discharge was of the 4th degree according to the Robert David Cerfolio Classification System. In the end, all 33 patients were discharged home with the Heimlich valve and treated on an outpatient basis. In a larger study involving 193 patients with PAL, R. J. Cerfolio et al. It was shown that 190 of them were cured without serious complications, and all 3 patients with complications had impaired immunity [57].

A retrospective review of prospectively collected data from 65 patients discharged with portable drainage devices found a decrease in DHSby an average of 3.65 days compared to the STS (Society of Thoracic Surgeons) database as a control [58]. Another retrospective analysis of the data of 73 patients discharged from the clinic over a 10-year period again showed a decrease in DHS (average 3.88 days) compared with the control group in the same institution (average 5.68 days). There was no increase in the number of complications in patients discharged with a portable drainage device, and only two patients required repeated hospitalizations [59].

In another study, PD was connected to the Heimlich valve on the 4th day of the postoperative period, and patients were discharged between 5 and 11 days of the postoperative period after learning how to check the air discharge, after which the drainage was removed. With PAL for more than 2 weeks, patients were hospitalized for provocative pinching of PD and resolving the issue of their removal [55]. Later R. J. Cerfolio et al. He reported connecting 193 patients to a portable drainage device on the 3rd day after surgery with discharge on the 4th day. All patients were discharged with the recommendation of oral antibiotics. Drains from the pleural cavity were removed on average 16.5 days after discharge, even in the presence of PAL or pneumothorax according to the results of the RGC [57]. A. M. Royer with col. the patients were examined within 3 days after discharge and all performed RGC. Drains from the pleural cavity were removed on average 4.7 days after discharge [58]. R. K. Schmocker and colleagues examined patients 4–5 days after discharge with the help of RGC and assessment of the presence of air discharge. Drains were removed an average of 8.3 days after discharge [59].

It is obvious that PAL negatively affects the timing of the start of adjuvant treatment [60]. Thus, there is retrospective evidence that patients can be safely discharged home with portable drainage devices. In most studies, patients were discharged on the 4th or 5th day after surgery, followed by follow-up for 3–5 days. Pleural drainage was usually removed within 4–11 days after discharge, and one study showed that all PD can be removed about 17 days after discharge, even in the presence of PAL or pneumothorax [59]. In the future, early identification of patients who can be discharged with portable drainage systems and forecasting the day of termination of air discharge will ensure timely discharge and follow-up planning, reducing the cost of medical care.

CONCLUSION

Thus, PAL after lung resection remains the most common postoperative complication in thoracic surgery. The analysis of modern literature indicates that digital drainage systems, providing objective, documented evidence of the cessation of air discharge, will be useful for the implementation of ERAS protocols aimed at the earliest possible removal of pleural drains. Clear evidence is presented that the use of active vacuum aspiration does not prevent air discharge, but possibly enhances it, therefore algorithms based on the experience of a particular institution will ensure optimal management of pleural drains, in particular, during the development of postoperative PAL. The use of routine RGC is minimized if there are no clinical indications. Pleurodesis with autologous blood appears to be the most promising minimally invasive way to eliminate PAL. At the same time, until its role is confirmed by a large-scale randomized clinical trial, there will remain a need for conservative management of PAL with early discharge of patients with portable drainage devices.

The latest advances in technology and evidence-based approaches in thoracic surgery provide a platform for eliminating contradictions in the postoperative care of patients who have undergone lung resection, creating a solid foundation for the development of algorithms to combat PAL.

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