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Title page

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Surgical Intervention Strategy for Postoperative Chylothorax After Lung Resection

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Abstract

Purpose The optimal surgical management of postoperative chylothorax has not been established. Thus, we evaluated the treatment strategy for postoperative chylothorax and identified associated predictors of surgical intervention.

Methods The subjects of this retrospective study were 50 patients who suffered postoperative chylothorax, representing 4% of 1235 patients who underwent pulmonary resection between 2008 and 2012. The chylothorax patients were classified into two groups based on their postoperative management: a conservative group and a surgical group. The following parameters were investigated to establish the predictors of surgical intervention for chylothorax: mode of surgery, preoperative complications, intraoperative management, and postoperative clinical status.

Results Forty-one (82%) patients were treated conservatively and 9 (18%) underwent reoperation, as direct or concomitant ligation of the thoracic duct at the point of leakage. The frequency of postoperative chest tube drainage just after initial surgery was significantly greater in the surgical group than the conservative group before oral intake was restarted (448 ± 189 ml/12h vs. 296 ± 117 ml/12h, respectively; p=0.003). Furthermore, it was a significant predictor of reoperation based on a multivariate analysis (p=0.010).

Conclusions The amount of chest tube drainage just after surgery and before oral intake was a useful predictor to help us decide on the need for early surgical intervention for postoperative chylothorax.

TEXT

Introduction

Postoperative chylothorax is a rare but well-known complication of general thoracic surgery. It results from a massive chyle leak caused by thoracic duct injury and is defined by the presence of chyle fluid, composed of rich triglycerides and chylomicrons in the pleural cavity [1]. This complication occurs following approximately 3% of general thoracic operations, especially those involving systematic mediastinal lymph node dissection [2, 3]. The standard treatments for postoperative chylothorax are space drainage, dietary management including a low fat diet, and surgical intervention [1, 4]. However, consensus has not yet been reached regarding the most appropriate surgical treatment strategies for this postoperative complication after lung resection because there are so few reports on this issue. Hence, investigating the clinicopathological characteristics of lung cancer patients to predict the outcomes of surgical intervention for prolonged chyle leakage is very important. We reviewed our experience of managing postoperative chylothorax after lung resection for primary lung cancer, evaluating our treatment strategies and identifying the predictors of suitability for early surgical intervention for prolonged chyle leakage.

Materials and methods

Among 1235 patients who underwent anatomical lung resection for primary lung cancers at our

department between January, 2008 and September, 2012, postoperative chylothorax developed in 50 (4%). We analyzed the clinicopathological and surgical characteristics of these 50 patients, who were the subjects of this retrospective study.

Postoperative management of chylothorax

Fig. 1 shows the management algorism to treat postoperative chylothorax after lung resection in our institute. Chest tubes were placed in all patients after lung resection. Moderate chest tube suction at -10 cm H2O was applied and the amount of drainage fluid was measured and recorded every 2 h until the morning of postoperative day (POD) 1 and every 8 h thereafter. Chest tubes were managed without suction after POD 1. All patients recommenced eating a normal diet from lunchtime on POD 1, at which time there was no evidence of postoperative chylothorax. Chylothorax was diagnosed by a milky pleural effusion and confirmed by an elevated triglyceride level of more than 110 mg/dL in the drainage fluid. We initially treated chylothorax patients conservatively, by commencing them on a low fat diet (fat intake < 20 g/day). If the chest tube drainage fluid did not decrease significantly despite this treatment, we stopped their oral intake completely and considered surgical intervention for prolonged chyle leakage. Surgical treatment was generally indicated if the daily chyle fluid did not decrease despite a low fat diet. If the chest tube drainage decreased slightly after the initiation of a low fat diet, we attempted pleurodesis by injecting a preparation of 5 kE OK-432 (Picibanil; Chugai Pharmaceutical Co Ltd, Tokyo, Japan) plus 10 ml 1% xilocaine plus 50 ml saline into the pleural space through the chest tube. If the chylothorax did not

resolve with conservative treatment within about 1 week after the initial surgery, we considered further surgical intervention. Chylothorax was considered cured if the chest tube drainage was serous and the output was < 200 ml/day. The patient was weaned off the chest tube, and remained on the low fat diet for 1 month.

Operative policy

The surgical procedure for lung cancer, mandatory for this study and performed in all patients, was anatomical lung resection. When chyle leakage during the course of the postoperative management was suspected, the patient was given a high fat ingredient several hours before reoperation to identify the chyle leakage point more effectively. The flow of chyle was increased by this method, rendering it easy to detect the point of chyle leakage during the reoperation in most cases. The principal surgical procedure for prolonged chyle leakage was direct ligation of the thoracic duct at the chyle leak point. We ligated the site of the fistula directly via thoracotomy. If the site of chyle leak was not identified, mass ligation of all tissues between the aorta, spine, esophagus, and azygos vein was performed at the level of the diaphragm.

Statistics

We reviewed our management of postoperative chylothorax. The medical records of these 50 patients were reviewed for age, gender, location of the tumor, clinical and pathological nodal stage, preoperative chemotherapy or chemoradiotherapy, surgical procedures including prophylactic ligation of the thoracic duct, amount of chest tube drainage fluid after lung resection, length of hospital stay, and

treatment course. The Chi-square test was used to compare two factors. Univariate and multivariate analyses were used to identify significant clinical factors that predicted surgical intervention for postoperative chylothorax in patients who underwent pulmonary resection with lymph node dissection for lung cancer, using Stat View 5.0 (SAS Institute). Forward and backward stepwise procedures were used to find the combination of factors that were essential for predicting prognosis. Statistical analysis was considered significant when the probability value was less than 0.05.

Results

Among 1235 patients who underwent anatomical lung resection for lung cancer, 50 (4%) suffered postoperative chylothorax. These patients comprised 35 men and 15 women, with a median age of 63 years (range: 33 to 81 years). Forty-two (84%) of the tumors were located on the right side, and 8 (16%) on the left side. The preoperative status of the lymph nodes was cN0-1 in 45 patients (90%) and cN2 in 5 patients (10%). One patient had received chemotherapy and one had received chemoradiotherapy, preoperatively. The initial surgical modes were pneumonectomy for 2 (4%) patients, bilobectomy for 5 (10%), lobectomy for 42 (84%; including sleeve lobectomy in 20%), and segmentectomy for 1 (2%). Systematic mediastinal lymph node dissection was performed for all patients, with prophylactic thoracic duct ligation to prevent postoperative chylothorax in 21 (42%) patients. The pathological nodal status was pN0-1 in 35 (70%) patients and pN2 in 15 (30%) patients. Table 1 summarizes the patient characteristics.

Most cases of chylothorax were diagnosed by POD 2 (range: POD 1 - 9).

Postoperative chylothorax was managed conservatively in 41 (82%) patients and their chest tubes were removed 5.5 days (range, 3-11) after the initial surgery. However, 11 (22%) of these 41 patients underwent pleurodesis using an OK432 mixture, because their drainage fluid decreased slightly following a low fat diet. The remaining nine (18%) patients underwent surgical intervention for prolonged chyle leakage following right lobectomy in eight and left pneumonectomy for lung cancer in one. The low fat diet did not decrease the amount of drainage fluid in seven patients, who required reoperation. One patient underwent pleurodesis before the reoperation because the drainage fluid was decreased slightly by the low fat diet and cessation of oral intake. Although the remaining patient ceased oral intake after the low fat diet, the amount of drainage fluid did not decrease and he required reoperation. Reoperation was performed a median of 5.5 days after diagnosis (range 3 to 12 days). The approach for reoperation was through the initial thoracotomy in eight patients and via video-assisted thoracic surgery in one. The points of chyle leak were detected in six patients (67%) through our strategy described in Methods and the thoracic duct was ligated at the level of the leak points in all six. Chyle leak points were detected at the point of dissection of station #4R lymph nodes (45%), station #2R lymph nodes (11%), and the adjacent point of prophylactic ligation of the thoracic duct (11%). Two other patients (22%) underwent mass ligation at the level of the diaphragm because their chyle leak points were not identified despite our preoperative strategy. Table 2 summarizes the management of the nine patients who underwent

reoperation to control chylothorax. The median duration of the second operation was 100 min (range, 70-134). The most difficult reoperation was on a patient in whom we found severe intrathoracic adhesion caused by the pleurodesis performed as conservative treatment, who underwent reoperation 12 days after the initial surgery. There were no major complications after reoperation in any of these patients. Prolonged chyle leakage was successfully managed by surgical intervention and the chest tubes were removed a median of 5.5 days (range; 5-14) after the initial surgery. The length of hospital stay from the diagnosis of chylothorax to discharge was 9.5 days (range; 7-19 days). No patient experienced recurrence of chylothorax after the second operation. There was no incidence of 30-day mortality or in-hospital death among the patients whose postoperative course was complicated by chylothorax.

We further classified the patients with postoperative chylothorax into two groups based on their management; namely, a conservative group and a surgical group, to identify the clinicopathological factors predictive of surgical intervention (Table 3). Prophylactic ligation of the thoracic duct was performed in 19 of 41 (46%) patients in the conservative group, but in only 2 of the 9 (22%) patients in the surgical group. However, there was no significant difference that accounted for a decrease in the number of patients that required reoperation for prolonged chylothorax ($p=0.184$). In contrast, postoperative drainage after a normal diet was greater in the surgical group than in the conservative group (825 ± 702 ml/day vs 444 ± 235 ml/day, respectively; $p=0.006$). Furthermore, postoperative drainage in the first 12 h after initial surgery (ml/12h) before starting oral intake was already significantly greater in

the surgical group than in the conservative group based on univariate analysis (448 ± 189 ml/h vs. 296 ± 117 ml/12h, respectively; p=0.003). Moreover, postoperative chest tube drainage for the first 12 h after the initial surgery was a significant predictor of reoperation for prolonged chyle leakage (p=0.010, Hazard Ratio 1.009, 95% confidence interval 1.00-1.02) based on multivariate analysis (Table 4). The amount of chest tube drainage in the 12 h after initial surgery exceeded 400 ml in 15 (30%) patients with postoperative chylothorax and the frequency was extremely high (68%) in the surgical group.

Discussion

Chylothorax is a relatively rare but serious complication, which results from thoracic duct injury, mainly due to definitive mediastinal lymph node dissection for lung cancer. The incidence of postoperative chylothorax following lung resection ranges between 0.25% and 3% [4, 5]. A previous study found that it developed more frequently in the right side of the chest, which may be related to the anatomy of the thoracic duct in the thoracic cavity [6]. The thoracic duct has variable anatomy in the thoracic cavity and it may be damaged by mediastinal lymph node dissection [7]. Mediastinal lymphadenectomy seems to be most responsible for the high incidence of postoperative chylothorax after lung resection. In our study, all patients with postoperative chylothorax underwent systematic mediastinal lymph node dissection. The most frequent chyle leak point was found during dissection of station #4R lymph nodes in our surgical group. The anatomic characteristics of the thoracic duct warrant special

attention to the postoperative chyle leak management for patients who undergo definitive mediastinal lymph node dissection.

Several researchers have discussed the management of postoperative chylothorax [3-5, 7-12]. The principles of conservative treatment include efficient drainage, sufficient inflation, and effective adhesion of the lung to decrease the dead space in the thoracic cavity, and restriction or cessation of flow through the thoracic duct to accelerate closure of the thoracic duct fistula, achieved by ceasing or restricting diet or/and parenteral nutrition. Conservative treatment is the first choice in many cases and the outcomes have been reported to be feasible [5, 10]. Some reports described that somatostatin injections effectively reduced chyle flow with total parenteral nutrition [13-14].

In the present series, 41 of 50 (82%) patients with postoperative chylothorax were able to be treated effectively by conservative treatment at our institution. Of these, 30 were treated by simply restricting their diet, whereas 11 needed pleurodesis. Although pleurodesis is an effective therapy for chylothorax, the fact that chyloma is a complication of pleurodesis must be remembered [15]. Furthermore, inadequate nutrition resulting from prolonged chyle leakage could compromise the patient's condition by depleting essential proteins, immunoglobulins, fat, vitamins, electrolytes, and water. Therefore, the timing for surgical intervention must be appropriate for persistent chyle leakage. In fact, early surgical management decreased the mortality rate for chylothorax [16]. Several studies recommended reoperation for postoperative chylothorax, in order to ligate the thoracic duct when conservative therapy was ineffective

[2, 4, 8]. Zabeck and colleagues reported that reoperation should be performed as soon as possible for postoperative chylothorax with chest tube drainage of more than 900 ml/day, because conservative management is unlikely to be successful [8]. Others recommended surgery for copious amounts of chest drainage exceeding 1500 ml/day in adults or more than 100 ml/kg body weight per day in children [11], chyle leakage at a rate of more than 1000 ml/day×5 days [17], or persistent chyle fluid for more than 2 weeks [18] despite conservative management.

In our institute, reoperation for postoperative chylothorax was indicated in the early postoperative phase, without pleurodesis, especially for patients with chest tube drainage of more than about 500 ml/day despite being on a low fat diet. As a result, the postoperative hospital stay did not differ significantly between the group of patients treated with pleurodesis and those treated with surgical intervention (11.3 ± 3.7 days vs 11.9 ± 4.3 days; Table 3), and the median hospital stay of our surgical group was shorter (median, 9.5 [range 7-19] days) than that of the groups who underwent reoperation in the studies of Kashiwanoha (19 [range 12–36] days) [2], and Heidelberg (26 [range 15–205] days) and (18 [range 11–30] days) [8]. These outcomes may be related to the early decision for surgical intervention based on the algorism for postoperative chylothorax management. Accordingly, all patients who underwent reoperation had no major complications after the second surgery.

The clinical parameters used to help decide on surgical intervention and the mode of intervention for prolonged chyle leakage vary among centers. This retrospective study showed that for increased chest

tube drainage fluid after initial surgery, reoperation for chylothorax needs to be performed more frequently. The amount of chest tube drainage in the first 12 h after the initial surgery prior to starting oral intake in the surgical group was significantly larger than that in the conservatively treated group. We found that if the thoracic duct injury was extensive in the initial surgery, chest tube output could increase even without any diet restrictions. Early monitoring of chest tube output helps us predict the need for reoperation to treat prolonged chyle leakage. Conventionally, we observed chest tube drainage after the patient started eating and then decided on the need for reoperation, in accordance with previous reports [2, 4, 8, 11, 17, 18]. However, our study showed that the drainage fluid in the first 12 h after the initial surgery before any food intake could also be an indicator of the need for reoperation. In other words, the amount of chest tube drainage fluid in the first 12 h after the initial lung resection might be a predictor of postoperative chylothorax that requires reoperation. This study shows that early surgical intervention for postoperative chylothorax is indicated for excessive chest tube drainage after the initial surgery.

This study has some limitations. First, the sample size was small because we investigated only patients with postoperative chylothorax. Second, this retrospective study showed the predictors of surgical intervention for prolonged chylothorax, but not the predictors of postoperative chylothorax. Finally, our study was retrospective and conducted a single institution. Consequently, a future prospective trial is warranted.

In conclusion, chyle leakage after pulmonary resection occurs as a result of injury to the main

thoracic duct or accessory lymphatic-venous connections around the azygos vein and carina, caused by definitive mediastinal lymph node dissection. The early decision to manage postoperative chylothorax is very important to maintain patient nutrition and prevent other complications. We found that the amount of chest tube drainage fluid in the first 12 h after lung resection was a useful clinical predictor of the need for early surgical intervention for postoperative chylothorax.

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Conflict of interest: none declared.

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Tables

Table 1 Clinical characteristics of the patients with postoperative chylothorax

Caracteristics	Value
Incidence	50/1,235 (4%)
Age	
Range (median)	33-81 (63)
Gender	
Male	35 (70%)
Female	15 (30%)
Tumor location	
Right	42 (84%)
Left	8 (16%)
Procedure	
Pneumonectomy	2 (4%)
Bilobectomy	5 (10%)
Lobectomy	42 (84%)
Sleeve lobectomy	10 (20%)
Segmentectomy	1 (2%)

Nodal status	
cN0-1	45 (90%)
cN2	5 (10%)
pN0-1	35 (70%)
pN2	15 (30%)
Preoerative therapy	
Chemotherapy	1 (2%)
Chemoradiotherapy	1 (2%)
Prophylactic ligation of the thoracic duct	21 (42%)

Table 2 Management and operative procedures performed for the nine patients who underwent reoperation for chylothorax

Initial operation	Conservative treatment	Leak point	Surgical Treatment
RUL	Low fat diet	Station #2R LN	Ligation of TD at the leak point
RLL	Low fat diet	Station #4R LN	Ligation of TD at the leak point
LP	Low fat diet	Not clearly	Ligation of TD at the carina
RUL with chest wall resection	Low fat diet	Station #4R LN	Ligation of TD at the leak point
Sleeve RMLL with PA plasty	Low fat diet	Not clearly	Ligation of TD at the diaphragm
RML	Low fat diet	Not clearly	Ligation of TD at the diaphragm
RLL	Low fat and cessation of diet, pleurodesis	Station #4R LN	Ligation of TD at the leak point
RUL	Low fat diet	Station #4R LN	Ligation of TD at the leak point
RUL	Low fat and cessation of diet	Adjacent PTD	Ligation of TD at the leak point

RUL = right upper lobectomy; RML = right middle lobectomy;

RLL = right lower lobectomy; LP = left pneumonectomy;

RMLL = right middle and lower lobectomy; LN = lymph node;

PA = pulmonary artery; TD = thoracic duct;

PTD=prophylactic ligation of thoracic duct;

Table 3 Characteristics of patients with postoperative chylothorax based on treatment procedures

Parameters	Conservative Group		Surgical Group	*P*-value
	(n = 41)		(n = 9)	
Age	61.4 ± 11.4		60.8 ± 9.2	0.872
Gender				0.574
Male	28		7	
Female	13		2	
Tumor location				0.553
Right	33		8	
Left	8		1	
Underwent upper lobectomy	24		4	0.441
Underwent sleeve lobectomy	8		2	0.854
Drainage in the first 12 h*	296 ± 117		448 ± 189	0.003
(ml/12hr)	Diet therapy	Pleurodesis		
	306 ± 123	271 ± 98		
Prophylactic ligation of TD	19		2	0.184
Diabetes mellitus	4		1	0.902

Heparinization	2		0	0.499
Postoperative hospital stay	9.1 ± 3.3		11.9 ± 4.3	0.035
(days)	Diet therapy	Pleurodesis		
	8.3 ± 2.8	11.3 ± 3.7		

* Postoperative thoracic drainage in the first 12 h, before oral intake.

TD = thoracic duct

Table 4 Multivariate analysis of predictors for surgical intervention in the patients with chylothorax

Parameters	Odds Ratio	95%CI	p-Value
Age	1.025	0.93 - 1.13	0.604
Gender (Male)	1.258	0.13 – 11.9	0.841
Tumor location (Right)	4.574	0.22 -93.3	0.423
Drainage in the first 12 h*	1.009	1.00 - 1.02	0.010
Prophylactic ligation of TD	0.223	0.03 - 1.72	0.150
Diabetes mellitus	0.991	0.06 – 18.0	0.995

CI = confidence interval; TD = thoracic duct

* Postoperative thoracic drainage in the first 12 h, before oral intake.

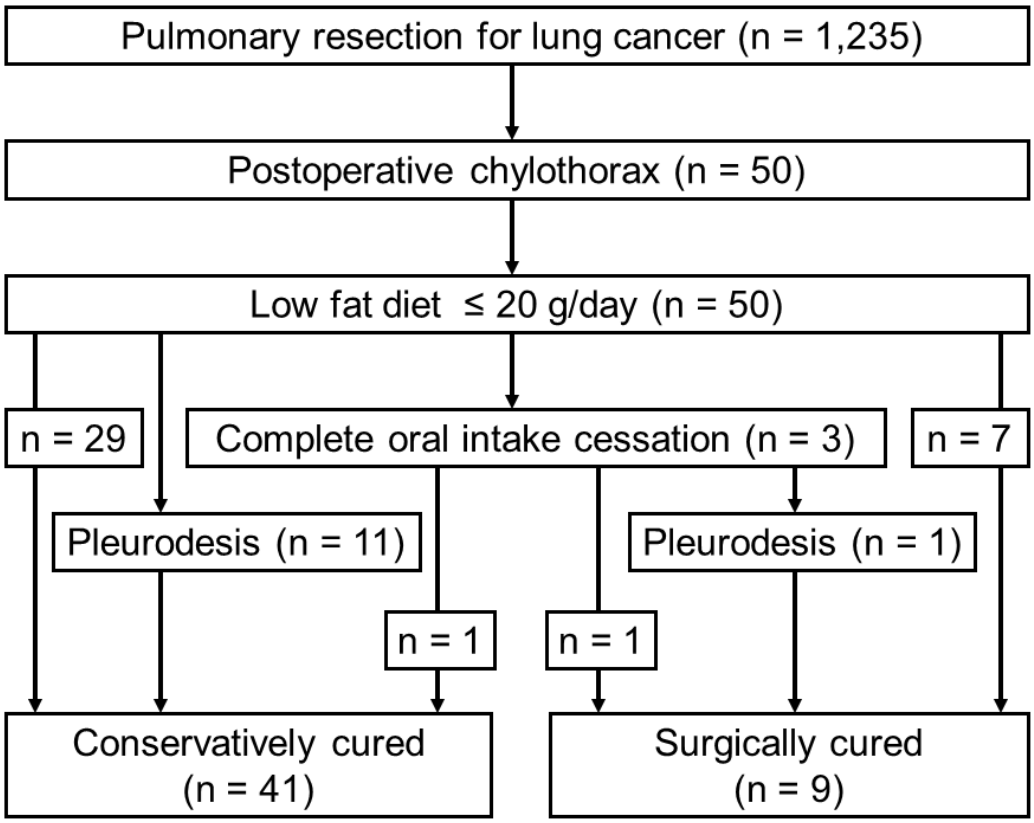
Pulmonary resection for lung cancer (n = 1,235)
Postoperative chylothorax (n = 50)
Low fat diet ≤ 20 g/day (n = 50)
n = 29
Complete oral intake cessation (n = 3)
n = 7
Pleurodesis (n = 11)
Pleurodesis (n = 1)
n = 1
n = 1
Conservatively cured (n = 41)
Surgically cured (n = 9)

Figure legends.

Fig.1 Our management schema for postoperative chylothorax.