JBUON 2020; 25(4): 1753-1760
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Prophylactic fat-free diet in patients undergoing lobectomy for lung cancer does not decrease postoperative chylothorax: Results from a single-center retrospective study

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Summary

Purpose: *Reliable measures to prevent chylothorax following lobectomy are lacking. Herein a case-control study was conducted to investigate the effect of prophylactic fat-free diet on the incidence of chylothorax after thoracoscopic lobectomy and systemic lymph node dissection (SLND) for lung cancer.*

Methods: *Between January 2015 and December 2017, the patients with primary non-small cell lung cancer who underwent lobectomy and SLND were retrospectively reviewed. Patients in the prophylactic group started fat-free diet one week before the surgery until removal of the chest tubes after the operation; while those in the control group took normal diet unless the onset of chylothorax. Logistic regression analysis was utilized to identify the predictive factors of chylothorax following lobectomy.*

Results: *The data of 110 patients in the control group and 115 cases in the prophylactic group were collected. The patients in prophylactic group showed less intraoperative blood loss [(79.9±48.7) mL vs. (100.9±55.6) mL, p=0.003], reduced postoperative drainage volume [(504.3±268.0) mL vs. (714.1±618.5) mL, p=0.001], and shorter chest tube duration [(3.6±1.7) days vs. (4.2±2.6) days, p=0.014]; however, a similar incidence of chylothorax [3 (2.6%) vs. 7 (6.4%), p=0.207] was recorded. Multivariate logistic regression analysis indicated that neoadjuvant therapy was an independent positive factor of chylothorax (odd ratio [OR] = 9.257; 95% confidence interval [CI] 1.434-59.773, p=0.019); whereas high-volume experience of the surgeon was an independent negative factor of this complication (OR = 0.129; 95% CI 0.017-0.982, p=0.048).*

Conclusion: *Prophylactic fat-free diet does not decrease the incidence of chylothorax after lobectomy. Further well-designed trials are warranted to verify this occasional finding.*

Key words: *fat-free diet, chylothorax, lobectomy, systemic lymph node dissection, lung cancer, three-dimensional computed tomography*

Introduction

Chylothorax after thoracic surgery may carry considerable morbidity if not diagnosed timely and treated properly [1]. A retrospective review indicated that the incidence of chylothorax following pulmonary resection and mediastinal lymph node dissection was 1.4% [2]. The management of chylothorax generally depends on nutrition control with pharmacological or surgical therapies; however, a clear consensus recommendation has yet to be reached. It is reported that low-fat diet and chemical pleurodesis are effective in > 80% of chylothorax patients after pulmonary resection [3]. If conservative therapy fails, surgical intervention might be needed.

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Received: 15/12/2018; Accepted: 21/02/2019

Prophylactic thoracic duct ligation has been examined, but to date it does not seem to reduce the incidence of chylothorax [1]. In addition, thoracic duct ligation might be correlated with reduced survival of the patients after esophagectomy for cancer [4]. Therefore, reliable prevention of chylous leakage necessitates further investigation.

As the major conservative therapeutic procedure for chylothorax is low-fat diet, we hypothesized that perioperative nutrition control in patients undergoing major thoracic surgery could minimize postoperative chyle leakage. Herein a retrospective cohort study was conducted to investigate the potential association of prophylactic fat-free diet and the incidence of chylothorax.

Methods

Our study had been approved by the Ethics Committee and Institutional Review Board of Xuzhou Central Hospital. Informed consent was obtained from every patient involved in this study. the data in this research were presented anonymously for privacy concern. Patients undergoing video-assisted thoracoscopic (VATS) lobectomy and mediastinal systemic lymph node dissection (SLND) for lung cancer between January 2015 and December 2017 were retrospectively reviewed. The inclusion criteria were as follows: (1) the tumor was localized without distal metastasis confirmed by chest and upper abdomen contrast-enhanced computed tomography (CT), brain magnetic resonance imaging and bone emission CT, (2) tumor stages I to III according to the 8th TNM staging system for lung cancer, (3) the American Society of Anesthesiologists score and cardiopulmonary function were sufficient for lobectomy, (4) patients undergoing standard lobectomy and SLND, and (5) pathological diagnosis of non-small cell lung cancer. The exclusion criteria were as follows: (1) previous thoracic operation or other cancer history, (2) thoracic duct ligation or resection in surgery for any reasons, and (3) the informed consent was not obtained. The process of data collection is shown in Figure 1.

The patients in control group took normal diet before and after the surgery until the diagnosis of chylothorax. On the contrary, the cases in the prophylactic group started fat-free diet one week before the surgery until the removal of chest tubes. Their perioperative parameters were recorded and compared. Primary observational parameter was the incidence of chylothorax, while the secondary parameters were the duration of postoperative chest drainage and overall drainage volume.

Enhanced recovery protocol

Fast-track protocol in thoracic surgery was performed individually. Pulmonary rehabilitation was conducted just after the admission of the patients. The clear fluid of maltodextrin solution was administered orally 6h (400 mL) and 2h (200 mL) before surgery respectively. Furthermore, multimodal analgesia was applied to improve pain relief with reduced side effects

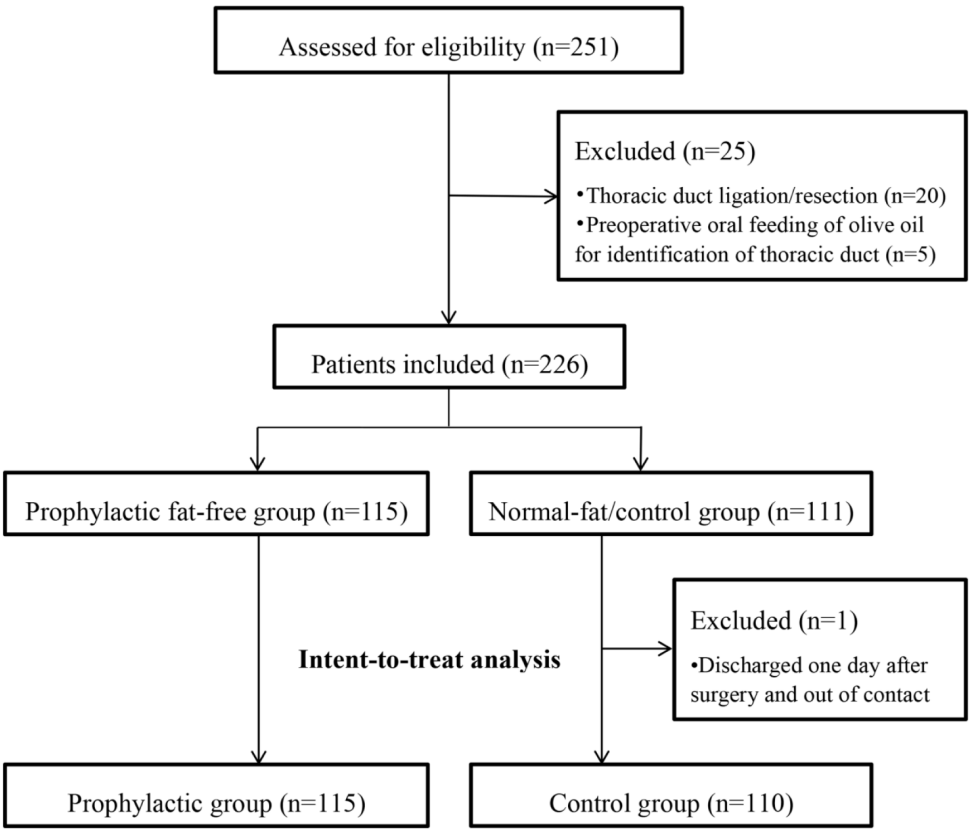

Figure 1. The flow chart of data collection.

after thoracic surgery [5]. Patient-controlled analgesia in combination with ultrasound-guided thoracic wall nerve block (serratus anterior plane block) was employed after surgery. Moreover, neostigmine and opioids were avoided [5]. The urethral catheter was removed when the patients were recovered from general anesthesia. Early mobilization out of bed and oral feeding with sufficient protein were initiated 6h after the surgery. Postoperative nausea or vomiting was strictly controlled by medical therapy such as ondansetron [6].

Preoperative surgical simulation

Three-dimensional computed tomography (3D-CT) angiography of the anatomic variations in the pulmonary vessels and resection simulation were performed individually before surgery. In detail, contrast-enhanced CT images were obtained using a multi-detector CT, and then the digital data at a slice thickness of 1.0 mm were transferred to a Macintosh platform (Apple, Cupertino, California) followed by a conversion to 3D-CT format by the free open-source software OsiriX (version 5.8.1). Accordingly, preoperative simulation of anatomical lobectomy was performed based on these 3D images.

Procedures of thoracoscopic lobectomy

All operations were performed under general anesthesia with one-lung ventilation, without the utilization of milk to facilitate the intraoperative identification of the thoracic duct. The surgical incision was made without rib spreading. For uniportal VATS, the incision was made in the 4th or 5th intercostal space along the anterior axillary line according to the location of the tumor (the 4th space for upper lobe and 5th space for middle/lower lobes). For two-port VATS, another observation incision was made through the 7th intercostal space along the middle axillary line. Pulmonary vessels, bronchi, and the fissures were divided sequentially using endoscopic staplers followed by standard mediastinal SLND. One 26 French chest tube was inserted for postoperative drainage. Thoracic duct ligation, mechanical or chemical pleurodesis during the operation was not performed in these cases.

Definition and management of chylothorax

Chylothorax was suspected when there was excessive chest drainage (>400 mL/day) with or without a milky appearance. Then it was diagnosed by presence of triglycerides (>110 mg/dL) and/or confirmation of chylomicrons (positive Sudan III stain) in the pleural fluid. A lipoprotein electrophoresis was the gold standard of its diagnosis [7]. The patients with chylothorax were initially treated conservatively, including octreotide (0.3 mg/day) and fat-free or low-fat diet (fat intake <10g/day). Moreover, if chest tube drainage produced >500

Table 1. Baseline characteristics of the patients

Characteristics	*Control group (n=110) n (%)*	*Prophylactic group (n=115) n (%)*	*p value*
Age, mean, years, Mean ± SD	63.0 ± 9.7	61.5 ± 10.1	0.232
≤ 60	40 (36.4)	44 (38.3)	0.769
> 60	70 (63.6)	71 (61.7)	
Gender			
Female	31 (28.2)	50 (43.5)	0.017
Male	79 (71.8)	65 (56.5)	
Body mass index, kg/m2, Mean ± SD	24.0 ± 2.8	24.0 ± 2.4	0.970
Normal (18.5-23.9)	56 (50.9)	62 (53.9)	0.652
Obesity or overweight (≥ 24)	54 (49.1)	53 (46.1)	
Smoking history			
Never	52 (47.3)	45 (39.1)	0.218
Previous	58 (52.7)	70 (60.9)	
Neoadjuvant chemo- or radiotherapy	27 (24.5)	15 (13.0)	0.027
Patients with comorbidity	58 (52.7)	70 (60.9)	0.218
Experience of the surgeons			
< 10 years in low-volume center	54 (49.1)	62 (53.9)	0.469
≥ 10 years in high-volume center	56 (50.9)	53 (46.1)	
Location of the tumor			
Upper lobe	51 (46.4)	41 (35.7)	0.102
Middle or lower lobe	59 (53.6)	74 (64.3)	
Clinical T stage of the tumor			
T1-2	55 (50.0)	61 (53.0)	0.648
T3-4	55 (50.0)	54 (47.0)	

Age is shown as the mean ± standard deviation (SD), and the categorical data are shown as number (%).

mL of chylous fluid during the first 24h after the initiation of the nutrition control, surgical intervention such as thoracic duct ligation or resection would be considered. Finally, the chest tube was removed if the effluent remained approximately ≤50 mL/day with or without chylothorax or ≤200mL when chylothorax was excluded. The patients were followed up for at least 3 months after surgery.

Statistics

Clinical features of the patients were recorded. Continuous data was presented as means ± standard deviations (SD). Statistical analysis was performed using Statistical Package for the Social Sciences software version 23.0 for Windows (SPSS Inc., Chicago, IL). Student's t-test or Wilcoxon test were used to compare continuous data, while Chi-square or Fisher's exact test were utilized for dichotomous or categorical variables. Potential risk factors of post-lobectomy chylothorax were assessed by stepwise multivariate logistic regression analysis, with chylothorax as the dependent variable and significance set at the 0.05 level. A two-sided p value of <0.05 was considered statistically significant.

Results

Patient demographics

From January 2015 to December 2017, the data of 225 patients who underwent lobectomy and mediastinal SLND for primary non-small cell lung cancer at our institution were collected and analyzed, with 144 male and 81 female cases. Comorbidities such as hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, emphysema, and bronchiectasis were calculated.

The mean age of patients in the two groups was 63.0±9.7 years and 61.5±10.1 years respectively. There was no significant difference in age (p=0.232), body mass index (p=0.970), smoking history (p=0.218), T stage (p=0.648) and location of the tumor (p=0.102), comorbidities (p=0.218), as well as distribution of experienced surgeons (p=0.469) between the two groups, except gender (p=0.017) and the proportion of neoadjuvant chemotherapy/radiotherapy (p=0.027), as shown

Table 2. Perioperative parameters of the patients

Variables	*Control group (n=110)*	*Prophylactic group (n=115)*	*p value*
3D-CTBA and resection simulation, n (%)	67 (60.9)	69 (60.0)	0.889
Surgical procedure, n (%)			
Two-portal VATS	18 (16.4)	20 (17.4)	0.870
Uniportal VATS	65 (59.1)	64 (55.6)	
Single-direction uniportal VATS, mean ± SD	27 (24.5)	31 (27.0)	
Lymph node dissections			
Stations	7.8±1.6	7.6±1.6	0.422
Numbers	12.7±2.5	13.1±2.6	0.249
Operation time, min	106.7±26.0	101.4±24.3	0.116
Blood loss, mL	100.9±55.6	79.9±48.7	0.003
Overall chest tube drainage, n (%)	32 (29.1)	27 (23.5)	0.339
Duration, days, mean ± SD	4.2±2.6	3.6±1.7	0.014
Total volume, mL, mean ± SD	714.1±618.5	504.3±268.0	0.001
Total postoperative complications, n (%)	32 (29.1)	27 (23.5)	0.339
Chylothorax,	7 (6.4)	3 (2.6)	0.207
Chest tube drainage, days, mean ± SD	10.6±2.1	8.3±1.5	0.135
Total volume, mL, mean ± SD	2692.9±728.8	1633.3±539.3	0.049
Pneumonia, n	6	2	
Aspiration, n	1	0	
Empyema, n	1	0	
Atelectasis, n	2	3	
Bronchopleural fistula, n	1	1	
Air leak > 7days, n	2	3	
Arrhythmia, n	12	15	
Postoperative hospital stay, days, mean ± SD	6.5±2.4	6.9±1.9	0.123

3D-CTBA: three-dimensional computed tomography bronchography and angiography; VATS: video-assisted thoracoscopic surgery; SD: standard deviation

in Table 1. In detail, 10 cases in the control group and 5 cases in the prophylactic group received induction therapy using gemcitabine plus cisplatin every 4 weeks for two cycles [8], while 14 cases in the control group and 6 cases in the prophylactic group used pemetrexed plus cisplatin every 4 weeks for two cycles. In addition, 3 cases in the control group and 4 cases in the prophylactic group underwent preoperative thoracic radiotherapy [9].

Operative features

Sixty-seven cases in the control group and 69 cases in the fat-free diet group performed 3D-CT bronchography and angiography before surgery. There were 18 (16.4%), 65 (59.1%) and 27 (24.5%) patients undergoing two-portal VATS, uniportal VATS, and single-direction uniportal VATS in the control group respectively. Meanwhile, there were 20 (17.4%), 64 (55.6%) and 31 (27.0%) patients undergoing two-portal VATS, uniportal VATS, and single-direction uniportal VATS in the fat-free diet group. All patients underwent standard lobectomy and SLND, without accidental injury of pulmonary or bronchial vessels or conversion to thoracotomy. There was no 30-day readmission or mortality during the follow up. Operative features of the patients are listed in Table 2.

As compared with the control, the patients in the prophylactic group demonstrated shorter chest tube duration [(3.6±1.7) days vs. (4.2±2.6) days, p=0.014], decreased total drainage volume [(504.3±268.0) mL vs. (714.1±618.5) mL, p=0.001] after surgery, and less estimated blood loss [(79.9±48.7) mL vs. (100.9±55.6) mL, p=0.003]. In addition, no significant differences were noticed in terms of 3D-CT bronchography and angiography, surgical procedure, operation time, postoperative hospital stay, stations and numbers of dissected lymph nodes, total postoperative complications, and postoperative hospital stay IN the two groups. Postoperative complications including pneumonia, aspiration, empyema, atelectasis, fistula, arrhythmia and prolonged air leak (>7 days) were calculated. Finally, a total of 32 (29.1%) and 27 (23.5%) cases of complications were observed in the control and prophylactic group respectively (p=0.339), as shown in Table 2.

Incidence and treatment of chylothorax

As shown in Table 3, a total of 10 cases (4.4%, 10/225) of chylothorax were confirmed in this cohort, with a median age of 60.6 years (range, 42-77). Among them, 5 cases received induction chemotherapy, while 2 cases received preoperative thoracic radiotherapy. The occurrence rate of chylothorax was similar in fat-free diet group and the control [2.6% (3/115) vs. 6.4% (7/110), p=0.207). Moreover, the patients with chylothorax in the prophylactic group indicated less drainage volume of pleural effusion as compared with those in the control [(1633.3±539.3) mL vs. (2692.9±728.8) mL, p=0.049], as shown in Table 2.

These 10 patients with chylothorax were treated conservatively with fat-free diet, in addition to percutaneous administration of octreotide (0.1 mg, every 8h). They resumed normal diet at a median of 9.9 days (range, 7-14) until the removal of the chest tubes, with an average chest drainage volume of 2375 mL (range, 1250-3600). Surgical intervention or readmission on the 3-month follow up was not reported.

Table 3. The clinical features of the 10 patients with postoperative chylothorax

No.	*Group*	*Age, years*	*Gender*	*Body mass index, Kg/m2*	*Induction therapy*	*Experience of the surgeon*	*Drainage, days*	*Drainage volume, mL*
1	Control	66	Male	21.4	Chemotherapy	High-volume	8	2300
2	Control	59	Female	25.0	Radiotherapy	Low-volume	9	1450
3	Control	73	Male	19.6	Chemotherapy	Low-volume	9	2600
4	Control	77	Female	24.1	Chemotherapy	High-volume	11	2750
5	Control	46	Male	24.2	None	Low-volume	11	2650
6	Control	42	Male	24.9	None	Low-volume	12	3500
7	Control	66	Male	26.3	None	Low-volume	14	3600
8	Prophylactic	61	Male	22.5	Chemotherapy	Low-volume	10	2250
9	Prophylactic	62	Male	25.1	Radiotherapy	Low-volume	8	1400
10	Prophylactic	54	Female	24.6	Chemotherapy	Low-volume	7	1250

These patients were treated conservatively using fat-free diet and percutaneous administration of octreotide (0.1 mg, every 8h) until the removal of chest tubes

Table 4. Multivariate analysis on the predictive factors of postoperative chylothorax

Variables	*OR (95%CI)*	*p value*
Age (> 60 years vs. ≤ 60 years)	2.086 (0.352-12.374)	0.418
Gender (female vs. male)	0.795 (0.136-4.649)	0.799
BMI (obesity or overweight vs. normal or lean)	4.803 (0.830-27.810)	0.080
Prophylactic fat-free diet (yes vs. no)	0.383 (0.067-2.186)	0.280
Experience of surgeons (high vs. low)	0.129 (0.017-0.982)	0.048
Smoking history (yes vs. no)	2.614 (0.312-21.865)	0.375
T stage of the tumor (T3-4 vs. T1-2)	0.813 (0.166-3.982)	0.799
Tumor location (middle or lower lobe vs. upper lobe)	2.097 (0.322-13.658)	0.439
Patients with comorbidity (yes vs. no)	2.139 (0.414-11.046)	0.364
Surgical procedures (Uniportal vs. Two-port VATS)	0.462 (0.050-4.286)	0.497
3D-CTBA and resection simulation (yes vs. no)	0.269 (0.038-1.928)	0.191
Induction chemotherapy or radiotherapy (yes vs. no)	9.257 (1.434-59.773)	0.019
Operation time (> 100 min vs. ≤ 100 min)	0.587 (0.112-3.083)	0.529
Stations of dissected lymph nodes (> 7 vs. ≤ 7)	1.533 (0.273-8.604)	0.627
Numbers of dissected lymph nodes (> 12 vs. ≤ 12)	0.430 (0.077-2.412)	0.338

OR: odds ratio; CI: confidence interval; VATS: video-assisted thoracoscopic surgery; 3D-CTBA: three-dimensional computed tomography bronchography and angiography

Logistic regression analysis for predictive factor of chylothorax

Table 1 summarized the patient features. Univariate analysis showed a noticeable difference in gender (p=0.017) and cases of preoperative chemo- or radiotherapy (p=0.027). Based on these findings, variables such as age, gender, body mass index, 3D-CT reconstruction and resection simulation, T staging and location of the tumors, experience of the surgeons, induction therapy, fat-free diet, operation time, stations and numbers of dissected lymph nodes were selected in multivariate logistic regression analysis.

The multivariate logistic analysis showed that the age (>60 years vs. ≤60 years), gender (female vs. male), body mass index (obesity or overweight vs. normal/lean), prophylactic fat-free diet (yes vs. no), smoking history (yes vs. no), surgical procedures (uniportal VATS vs. two-portal VATS), 3D-CT reconstruction and resection simulation (yes vs. no), T stage (T3-4 vs. T1-2) and location (middle or lower lobe vs. upper lobe) of the tumor, operation time (>100 min vs. ≤100 min), stations (> 7 vs. ≤7) as well as numbers (>12 vs. ≤12) of dissected lymph nodes were not significantly correlated with the incidence of chylothorax (Table 4). Moreover, induction therapy [odds ratio (OR) =9.257; 95% confidence interval (CI) 1.434-59.773, p=0.019] was identified as independent risk factor of post-lobectomy chylothorax; whereas high-volume experience of the surgeon (OR=0.129; 95% CI 0.017-0.982, p=0.048) might be correlated with decreased incidence of this complication.

Discussion

Chylothorax associated with pulmonary resection for lung cancer is infrequent. Right-sided chylothorax is more common than left-sided chylothorax complicating pulmonary resection for lung cancer [10]. There are several issues needing elucidation accordingly.

First, as shown in this cohort, fat-free diet is correlated with decreased postoperative chest drainage but not the occurrence rate of chylothorax. Although low-fat diet is the major conservative management of thoracic surgery-related chylous leakage and it is mainly effective, the present study showed that prophylactic fat-free diet in patients undergoing lobectomy and SLND did not display a significant preventive role. Meanwhile, the long-term potential harm of fat-free diet on patients' immune function requires further investigation.

Second, chylous leakage results in immune deficiency, nutritional depletion because of the rapid loss of proteins, fat-soluble vitamins, lipids and electrolytes and impaired respiratory function [11], necessitating quick closure of the leak. Therefore, rapid identification of chylothorax is crucial for timely management and prognosis. The typical manifestations of chylothorax are dyspnea, chest pain, cough and fatigue. The optimal surgical management of chylothorax has not been established [12]. It can be managed initially with conservative approaches with a mortality rate of 1% [13], including somatostatin and avoidance of fat intake. Etilefrine is also effective for chylothorax in patients after thoracic duct resection

[14]. Chemical pleurodesis alone or combined with thoracic duct ligation is the second-line treatment option. Fibrin glue infiltrating the leak site is effective when the exact leak site cannot be identified [7]. However, to date there is no consensus on the optimal management of high-output chylothorax (≥1,100 mL in 24 h). An intention-to-treat analysis showed that surgical duct ligation was more effective, and lymphangiography may be helpful to determine which patients were suitable for ligation or embolization [13]. Surgical intervention can be earlier if pleural drainage does not decrease when treated conservatively [15]. Furthermore, if the chylous leakage cannot be well visualized and positioned, thoracic duct ligation via VATS may be needed [7].

Moreover, thoracoscopic lobectomy as a minimally invasive approach is widely utilized for pathological stage II or IIIA lung cancer, with similar postoperative complications as compared with thoracotomy [16]. As shown in our study, a large proportion of lung cancer patients underwent lobectomy and SLND using uniportal VATS. There was no conversion to thoracotomy or 30-day mortality after surgery, without compromised lymph node dissection.

Third, the elucidation of predictive factors of chylothorax is helpful to establish the optimal perioperative management. Post-chemoradiotherapy and high intraoperative fluid balance are predictors of chylothorax after esophagectomy [17]. In the present study, 27 patients in the control group and 15 cases in the prophylactic group underwent neoadjuvant chemotherapy or radiotherapy. Our study indicated that induction chemotherapy or radiotherapy before surgery was an independent risk factor of chylothorax after lobectomy and SLND. Therefore, the patients undergoing induction treatment should be monitored carefully, and the exclusion of chyle could be considered as a precondition of chest tube removal. Meanwhile, high-volume experience of the surgeon is an independent protective factor of chylothorax. Based on these results, postoperative chyle leakage is probably mainly a technical issue, and the specific skills should be elucidated and simplified for education of the young surgeons.

On the other hand, fat-free diet is not beneficial for intraoperative identification of thoracic duct. Previous studies showed that preoperative fat loading is significantly associated with intraoperative visualization of the chyle leak. For example, the administration of olive oil before surgery facilitates the identification of thoracic duct and decreases chylothorax after esophagectomy [18]. According to a meta-analysis, prophylactic ligation of the thoracic duct is effective to reduce the incidence of chylothorax after esophagectomy [19]; however, it should be interpreted with caution due to the publication bias and generally low quality of the included studies. A newly reported study shows that prophylactic thoracic duct ligation does not reduce the incidence of chylothorax [20]. Another meta-analysis also indicates that prophylactic thoracic duct ligation does not lower the incidence of chylothorax following esophagectomy [21]. Therefore, further high-quality researches are still warranted.

The present study has certain limitations. First, this is a retrospective and nonrandomized study with obvious heterogeneity, including gender bias and different proportion of cases undergoing induction therapy. Second, the sample size is small and the incidence of postoperative chylothorax is low in a single institution. Moreover, there may have been some inherent bias caused by the surgical experience, technical skills, and preference of the surgeons. Further researches exploring the preventive methods of chylous leakage are warmly welcomed.

In summary, this study suggests that prophylactic fat-free diet in lung cancer patients undergoing lobectomy and SLND does not decrease the incidence of chylothorax; however, the retrospective nature and heterogeneities should be considered when interpreting the results. High-quality randomized controlled trials are warranted before a definite conclusion could be drawn.

Acknowledgements

We would like to thank the editors of J BUON for their kind advices and great contribution in editing this manuscript.

Conflict of interests

The authors declare no conflict of interests.

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