

Original Article

Non-prophylactic thoracic duct ligation may be favorable prognosis factor for post-esophagectomy chylous leakage undergoing lymphangiography

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Abstract: Purpose: To determine the clinical factors that affect therapeutic effects of lymphangiography (LAG) on post-esophagectomy chylous leakage. Methods: We retrospectively reviewed 1198 patients undergoing esophagectomy from 2007 to 2017 in our hospital. Two patients with post-esophagectomy chylous leakage undergoing LAG were identified. One patient received non-prophylactic thoracic duct ligation during esophagectomy and was cured by LAG after non-effective conservative treatment. Another patient was prophylactically ligated and failed to be cured by LAG but cured by re-surgery. The clinical course of these patients was compared to reveal the factors related to the therapeutic effects of LAG for post-esophagectomy chylous leakage. Furthermore, we conducted a systematic literature review in four English databases (EMBASE, OVID, ISI Web of Science, and PubMed) with the date from January 2000 to December 2018 to summarize the lymphangiography management of post-esophagectomy chylous leakage. Combining with our study, a total of 15 studies containing 42 cases were included. Results: After comparing the clinical course of the two cases in our study, we speculated that LAG was more therapeutically effective for post-esophagectomy chylous leakage in patients without prophylactic thoracic duct ligation. Analysis of the cases from our study and the previous studies suggested that the patients without prophylactic thoracic duct ligation needed less reoperation than those with thoracic duct ligation (9.09% versus 53.33%) after LAG management. And the patients with 500 ml/d pleural effusion (PE) before LAG were more likely to be healed by LAG alone than those with 500~1000 ml/d or > 1000 ml/d PE before LAG (76.92% versus 35.71% and 14.29%). Conclusions: Non-prophylactic thoracic duct ligation and less PE might be favorable factors in predicting therapeutic effects of LAG in chylous leakage after esophagectomy.

Keywords: Chylous leakage, esophagectomy, thoracic duct preservation, lymphangiography, therapy

Introduction

Prophylactic thoracic duct ligation is a routine operation step in esophagectomy and has been considered as an effective method to reduce the incidence of postoperative chylous leakage in the past decades [1-3]. Esophagus is close to thoracic duct in thoracic cavity and iatrogenic thoracic duct injury may occur when resecting esophageal lesions during esophagectomy, leading to a postoperative chylous leakage [4]. Chylous leakage brings various complications including long-term and bigger thoracic cavity drainage, postoperative malnutrition, sepsis,

and immunosuppression, thus affecting the recovery of patients as well as increasing the mortality [5, 6].

Post-esophagectomy chylous leakage is a rare complication with an incidence of 2.7% to 3.8% [7]. Thus, prompt and aggressive interventions are always needed for the management of chylous leakage. Conservative treatments including intravenous nutrition, pleural drainage, and somatostatin should be given in the first place [8-10]. Most patients with chylous leakage will improve gradually after conservative treatments [8-10]. If these treatments are not effec-

tive, a second surgery is often required to ligate the thoracic duct [11]. However, surgical treatment is highly invasive for chylous leakage patients because they are frequently in poor nutritional and immunosuppressive conditions. Lymphangiography (LAG) has been used to identify leakage sites of chylous in past [12]. Recent reports also reveal the therapeutic value of LAG in management of conventionally untreatable chylous leakage [12-15].

Here, we retrospectively analyzed the treatments and outcomes of refractory chylous leakage after esophagectomy in our center in recent 10 years and combined a systematic literature review to investigate the therapeutic effects of LAG in management of post-esophagectomy chylous leakage.

Patients and methods

Patients

A retrospective analysis of 1198 patients with esophageal cancer undergoing esophagectomy from 2007 to 2017 in our hospital, Beijing Cancer Hospital & Institute, Beijing, China, was performed. The patients with post-esophagectomy chylous leakage who were treated with lymphangiography were screened and enrolled. Clinical data of the patients were collected. The study was approved by our institute.

Pedal lymphangiography procedure

The lymphangiography was performed by interventional radiologists. Briefly, 1.5 ml of a mixture consisting of methylene blue and 2% lidocaine (1:1) was injected subcutaneously between right toes roots, and local anesthesia with 1% lidocaine was performed in the middle of right acrotarsium under microscope. Then, a skin incision with the length of 1 cm was made and a blue-stained lymphatic vessel was exposed and cannulated with an angiography puncture needle. 12 ml of iodinated oil was injected with an automatic injector at a rate of 8 ml/h. Chest and abdominal radiographs and computed tomography (CT) images were obtained to observe lymphatic channels and chylous leakage.

Systematic literature search

To summarize the lymphangiography management of chylous leakage after esophagectomy,

we performed a systematic literature screening in four English databases (EMBASE, OVID, ISI Web of Science, and PubMed) with the date from January 2000 to December 2018 according to PRISMA guidelines. The following searching key words were used: “chylothorax OR chyle OR chylous leakage”, “lymphangiography”, and “esophageal cancer OR esophagectomy”. Inclusion criteria: (1) language was limited to English; (2) the patient was diagnosed as post-esophagectomy chylothorax, chyle, or chylous leakage and underwent lymphangiography; (3) full peer reviewed papers that have been published as full texts including case report, case series, and research article. Exclusion criteria: (1) studies with overlapped or insufficient data; (2) re-surgery was performed immediately after LAG; (3) studies that the data related to chylous leakage after esophagectomy could not be separated; (4) patients were treated with both LAG and thoracic duct embolisation (TDE); (5) patients were treated with LAG but LAG was not completed or failed; (6) abstract, review or meeting articles. The clinicopathological information including thoracic duct was resected or not, amount of pleural effusion before and after conventional treatment, conservative treatment strategy, amount of pleural effusion before lymphangiography, the interval between esophagectomy and lymphangiography, pleural effusion after lymphangiography, and additional treatment and outcomes at follow up were collected. Chi-square test and Fisher's exact test were used to determine the associations of different characteristics with clinical outcomes of the patients with post-esophagectomy chylous leakage undergoing LAG.

Results

Patients

From 2007 to 2017, 1198 patients with esophageal cancer underwent esophagectomy at our hospital were reviewed. Of these patients, four patients suffered from chylous leakage after esophagectomy, with a very rare prevalence. Of the four patients, one patient was cured by conservative treatment, one patient was cured by second surgery, one patient was treated with second surgery and lymphangiography, but failed, and finally cured by a third surgery, and one patient was cured by lymphangiography. To investigate the factors that affected the therapeutic effectiveness of lymphangiography on post-esophagectomy chylous leakage, we re-

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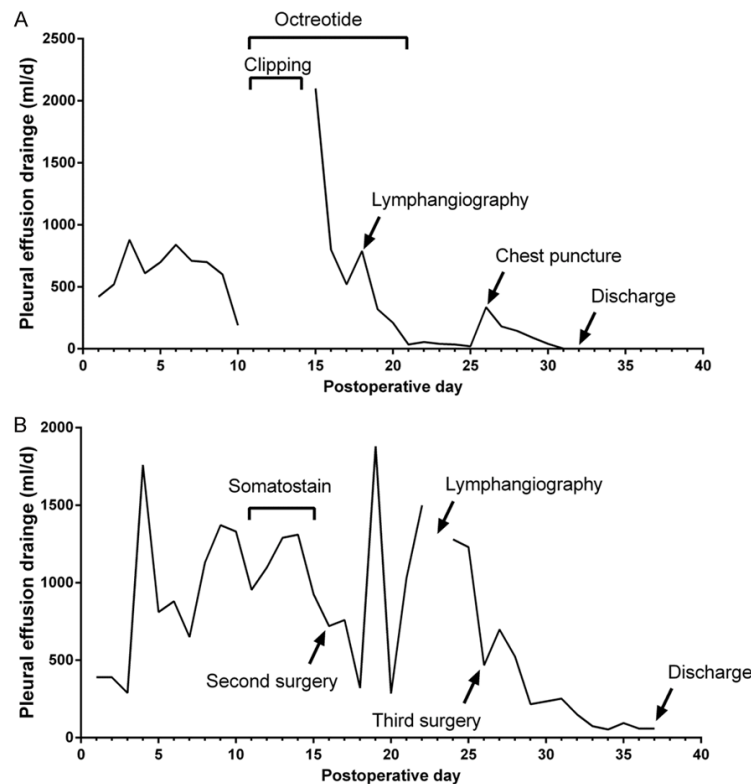


Figure 1. Clinical course of case 1 (A) and case 2 (B).

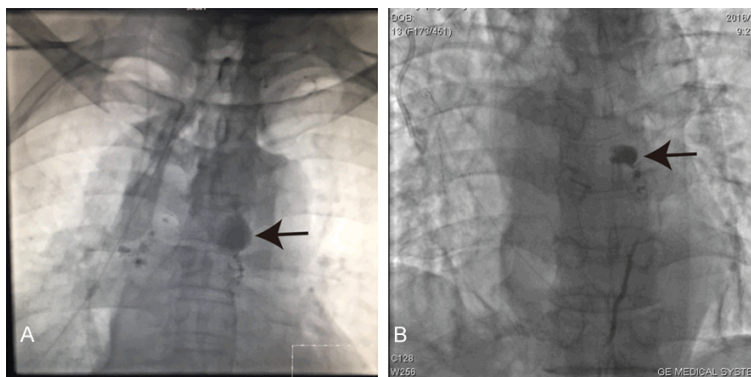


Figure 2. Lipiodol lymphangiography of case 1 (A) and case 2 (B). Arrow, thoracic duct injury.

viewed the clinical course of the two patients receiving lymphangiography.

Outcomes of chylous leakage after esophagectomy underwent lymphangiography

Case 1 was a 67-year-old male patient who was admitted to our hospital due to esophageal mass after eating difficultly for one month. Gastroscopy examination revealed a flat tumor of the mucosa at 27-29 cm from the incisors.

Pathological results suggested it was at least an in situ squamous cell carcinoma. Chest computed tomography (CT) suggested that a suspicious thickness was found in mid-esophagus. Then angiography was performed and it was found that the wall of the esophagus abdominal segment was rigid, the cavity was narrow with a range of 7 mm, the mucosa was damaged, the shadow was observed, and the barium was slightly blocked. Finally, a cT1aN0M0 stage IA esophageal squamous cell carcinoma was diagnosed. Thereafter, the patient received esophagectomy under general anesthesia. The thoracic duct was preserved during the operation and was not prophylactically ligated. There was no apparent complication during the surgery and no intraoperative chyle leakage was observed. Postoperatively, an increased amount of pleural effusion discharge (190-880 ml/d) flowed continuously from the chest drainage tube (**Figure 1A**). On the eleventh postoperative day (POD11), the patient underwent conservative treatments including total parenteral nutrition and octreotide, however, the chylous leakage was not improved with chest drain output of 520-2100 ml/d. On POD18, pedal lipiodol lymphangiography was performed (12 ml lipiodol, 8 ml/h) (**Figure 2A**). Lipiodol also entered into

the thoracic duct above the leakage site, indicating no much pressure existed in the leakage site. After lymphangiography, the chest discharge decreased dramatically to 55 ml/d on POD21, i.e. the third day post lymphangiography. The mean amount of chest drainage was 738 ml/d before lymphangiography and 116 ml/d after lymphangiography. The chest drain tube was removed on POD31 and the patient was discharged on POD32.

The second case was a 73-year-old man with feeding obstruction for 4 months and was referred to our hospital. Protruded type change of the mucosa at 27-31 cm from the incisors and suspicious thickness in mid-esophagus were demonstrated by gastroscope and chest CT examination. Angiography suggested that the wall of the cavity in the esophagus abdominal segment around cardia was rigid and the lumen was narrow. Damage mucosa and shadow was also observed. The barium was slightly blocked. Ultimately, a cT1NOMO, stage IA epithelial esophageal squamous cell carcinoma with high grade was identified. Then esophagectomy under general anesthesia was performed. The thoracic duct was also resected and prophylactically ligated during the surgery. After operation, chylous leakage was found and the chest drain output increased to 650-1760 ml/d from POD4 (**Figure 1B**). Conservative treatment was first given and somatostatin was administered on POD11 to POD16. Unfortunately, the chylous pleural effusion was not controlled. On POD16, second surgery was performed to detect the leakage site and ligate thoracic duct. However, the pleural effusion was not reduced significantly except a transient decrease. Pedal lipiodol lymphangiography was carried out on POD24 and the contrast media was leaked at the thoracic segment of the duct while the thoracic duct above the leakage site was not visible under the LAG, suggesting a great pressure at the leakage site (**Figure 2B**). But inconsistent with the expectation, the chest discharge was not reduced significantly. Finally, the chylous leakage was cured by a third surgery on POD26 and the chest drain tube was removed on POD37. After reviewing the clinical course of our two cases, we speculated that the prophylactical ligation of thoracic duct during the esophagectomy was a crucial factor that determined the therapeutic effects of lipiodol LAG in chylous leakage.

Systematic literature review

To determine the factors that influenced therapeutic effects of lipiodol LAG for chylous leakage after esophagectomy, we performed a systematical search of the related literature in PubMed, OVID, Embase, and ISI Web of Science databases. **Figure 3** showed the literature searching and screening process. A total of 222 documents were initially retrieved from the four English databases and additional sources.

After excluding the duplicated papers, review or meeting abstracts, and irrelevant articles, 28 articles were left for further screening. Then 14 articles were excluded, of which, four contained no sufficient data, surgery was performed immediately after LAG in three articles, chylous leakage after esophagectomy could not be separated in four articles, LAG and thoracic duct embolisation were performed at the same time in two articles, and LAG was not technically successfully in one article. Combined with our present study, a total of 15 studies containing 42 cases were finally included [12, 14-26] (**Table 1**). 33 cases were male and nine were female and their average age was 64.95 years. Thoracic duct was resected and ligated during esophagectomy or ligated in reoperation before LAG in 15 cases and preserved in 11 cases. The mean pleural effusion volume (PE) before LAG was ≤ 500 ml/d in 13 cases, 500~1000 ml/d in 14 cases, and ≥ 1000 ml/d in 14 cases. 18 patients were cured by LAG alone. Pleurodesis, thoracic duct embolization or disruption were further performed after LAG in 11 patients, and reoperation was performed in 13 patients to ligate the thoracic duct. Associations of the clinical factors including age, gender, thoracic duct ligation before LAG, and PE before LAG, with prognosis in LAG treated chylous leakage after esophagectomy were determined by Chi-square test or Fisher's exact test. There were no significant associations of clinical outcome with age and gender in LAG treated chylous leakage after esophagectomy. The patients without thoracic duct ligation before LAG needed less reoperation (9.09% versus 53.33%; $P = 0.051$; **Table 2**), suggesting preservation of thoracic duct was a favorable factor for the outcomes of LAG treated chylous leakage. More than 50% PE change before and after LAG was more prevalent in patients with ≤ 500 ml/d PE before LAG than those with 500~1000 ml/d or 1000 ml/d PE before LAG (90.91% versus 45.45% and 41.67%; $P = 0.031$; **Table 2**). And the patients with ≤ 500 ml/d PE before LAG were more likely to be healed by LAG alone than those with 500~1000 ml/d or ≥ 1000 ml/d PE before LAG (76.92% versus 35.71% and 14.29%; $P = 0.021$; **Table 2**).

Discussion

Undiagnosed postoperative chylous leakage may lead to malnutrition, sepsis, and a high

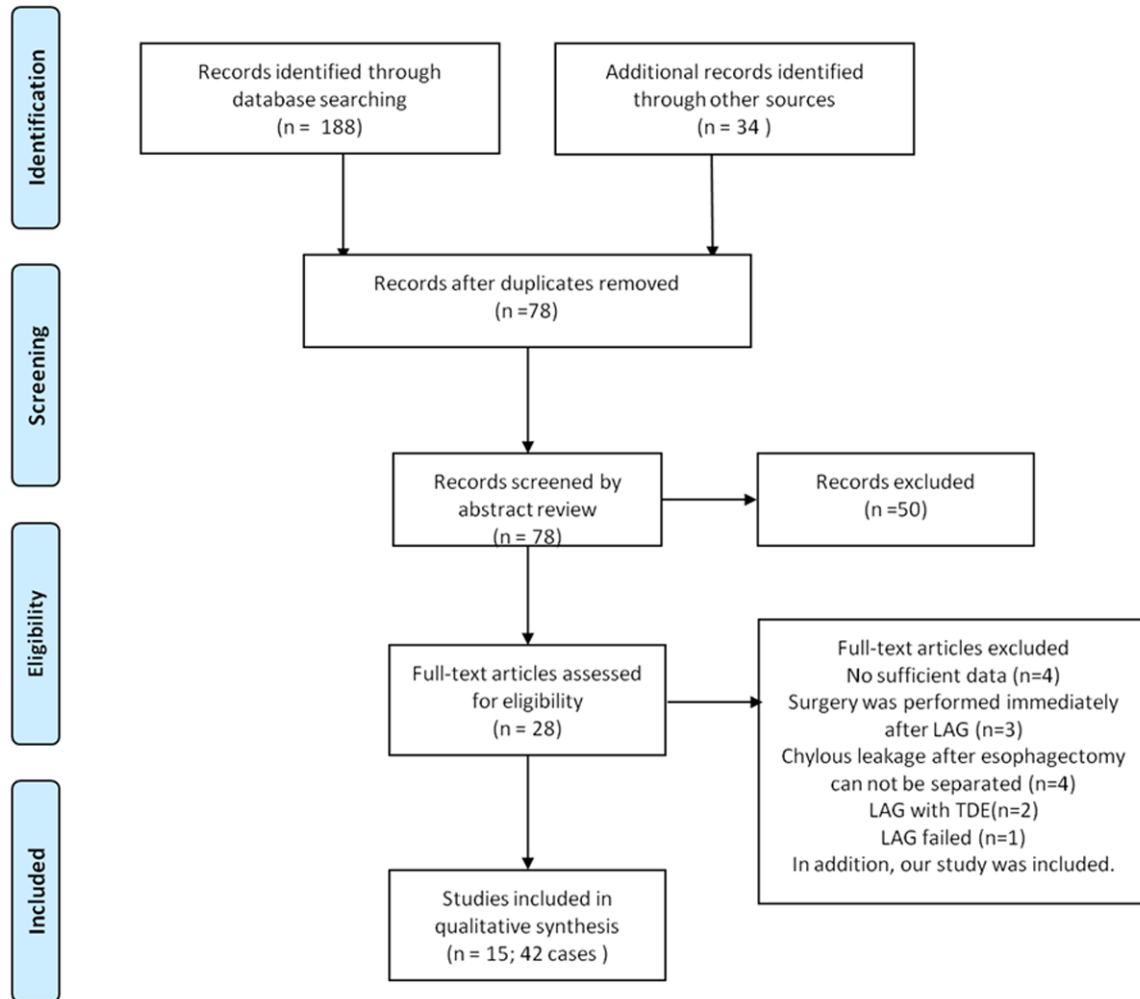


Figure 3. Literature searching and screening flow diagram. Abbreviations: LAG, lymphangiography; TDE, thoracic duct embolisation.

mortality rate, thus, an optimum management is required. Conservative treatments including total parental nutrition, octreotide administration, and chemical pleurodesis have been used to reduce the pleural effusion. If the chylous leakage is refractory to conservative treatments, more invasive treatments should be considered, such as ligation or clipping under thoracotomy or thoracoscopy and percutaneous thoracic duct embolization [27]. Lymphangiography with lipiodol is used as a diagnostic tool to detect leakage sites and anatomical variations in the thoracic duct and lymphatic channels [12]. Recently, lipiodol lymphangiography (LAG) also exhibits a therapeutic effect in reducing chylous leakage in some cases that allows surgery to be avoided. It is necessary to explore the timing of LAG and to predict the

therapeutic effects in patients with post-esophagectomy chylous leakage undergoing LAG. Here, we presented the application of lipiodol LAG in management of chylous leakage after esophagectomy in two cases and the clinical outcomes.

In our case 1 with chylous leakage after esophagectomy, the conservative treatment was not effective and pedal lipiodol LAG was subsequently performed. After lymphangiography, the chest discharge decreased dramatically to 55 ml/d and the chylous leakage was cured. In contrast, in case 2, the amount of chest drainage was not reduced and reoperation was performed to ligate the thoracic duct. After reviewing the clinical course of our two cases, we speculated that the ligation of thoracic duct

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Table 1. Clinical characteristics and outcomes of patients with chylous leakage after esophagectomy underwent lymphangiography

Reference	Case	Age (yrs.)	Gender	Thoracic duct	PE before LAG (ml/day)	LAG date (POD)	PE after LAG (ml/day)	Additional treatments after LAG
Mine et al, 2008	1	58	M	Resected	800-1000	NA	800-1000	Ligation
Matsumoto et al, 2009	1	61	M	NA	500	21	100	Healed
	2	55	M	NA	500	10	50	Healed
	3	71	M	NA	300	35	50	Healed
	4	55	F	NA	150	35	60	Healed
Kaburagi et al, 2012	1	65	M	Resected	1547	8	1606	Ligation
Kawasaki et al, 2013	1	68	M	Resected	700	30	700	Pleurodesis
	2	63	M	Preserved	2200	21	2800	Ligation
	3	61	F	Resected	800	62	870	Ligation
	4	72	M	Resected	300	7	100	Healed
	5	65	F	Resected	600	3	122	Healed
	6	63	F	Resected	850	12	1100	Ligation
	7	59	M	Resected	300	28	1100	Ligation
Ramzi et al, 2013	1	56	M	NA	2000	20	NA	Ligation
	2	79	M	Preserved	560	NA	NA	Healed
	3	55	M	NA	1500	30	NA	ligation but failed then medical treatment
Yoshimatsu et al, 2013	1	74	M	NA	2000	NA	2000	Ligation
	2	72	F	NA	1000	NA	450	Healed
	4	71	M	NA	NA	NA	NA	Healed
	5	55	F	NA	150	NA	60	Healed
	6	55	M	NA	500	NA	50	Healed
	1	61	M	Preserved	400	97	20	Second LAG
Yamamoto et al, 2015	1	62	M	Resected	1200	15	100	Healed
Abe et al, 2016	1	69	M	Resected	2000-2850	6	2000	Ligation with VATS
	2	53	M	Resected	≥ 1000	15	≤ 500	Pleurodesis with OK432
	3	68	M	Preserved	500-1000	15	≤ 500	Pleurodesis with OK432
	4	62	M	Resected	≥ 1000	31	≤ 500	Healed
	5	70	M	Preserved	≥ 1000	12	≥ 1000	Clipping leakage site with CATS
	6	64	F	Resected	≥ 1000	21	≤ 500	Pleurodesis with OK432
	7	69	M	Preserved	≥ 1000	10	500-1000	Pleurodesis with OK432
	8	74	M	Preserved	500-1000	19	≤ 500	Healed
	9	54	F	Preserved	≤ 500	23	≤ 500	Pleurodesis with OK432
Liu et al, 2016	1	67	M	NA	788	93	963	Ligation
	2	59	M	NA	1500	12	1350	Ligation
	3	75	M	NA	1000	21	275	Healed
Navarrete et al, 2016	1	64	M	Preserved	391	7	78	Healed
Shimakawa et al, 2017	1	73	M	Ligation	1600	24	2000	Ligation
Tumura et al, 2017	1	70	M	Preserved	236	8	6	Healed
Yannes et al, 2017	1	67	F	NA	350	13	NA	Healed
	2	74	M	NA	600	12	NA	TDD
Present study	1	67	M	Preserved	738	18	116	Healed
	2	73	M	Resected	963	24	1225	Ligation

Abbreviation: NA, not applicable; M, Male; F, Female; PE, pleural effusion; LAG, lymphangiography; POD, postoperative day; TDD, thoracic duct disruption.

during the esophagectomy was a crucial factor that determined the therapeutic effects of lipiodol LAG for chylous leakage. In case 1, the thoracic duct was preserved and not prophylactically ligated and the pressure at the leakage site was small. The pooling of lipiodol surround-

ing the leakage site might induce a local inflammatory reaction, which could result in closure of the leak by acting as an embolic agent [5, 28]. Conversely, the inflammatory reaction induced by lipiodol in leakage site of case 2 was not sufficient to block the leakage due to

Table 2. Pooling analysis of the patients with chylous leakage after esophagectomy underwent lymphangiography

Parameters		PE change				Clinical outcomes				
		≥ 50%	<50%	Chi-square	P-value	Healed	Minimal invasive procedure	Reoperation	Chi-square	P-value
Age	< 65 yrs	12	6	0.971	0.324	8	5	7	0.295	0.863
		66.67%	33.33%			40.00%	25.00%	35.00%		
	≥ 65 yrs	8	8			10	6	6		
		50.00%	50.00%			45.45%	27.27%	27.27%		
Gender	Male	15	12	0.672	0.672	13	9	11	0.782	0.676
		55.56%	44.44%			39.39%	27.27%	33.33%		
	Female	5	2			5	2	2		
		71.43%	28.57%			55.56%	22.22%	22.22%		
TGL	Yes	6	9	0.361	0.361	4	3	8	5.970	0.051
		40.00%	60.00%			26.67%	20.00%	53.33%		
	No	5	2			4	6	1		
		71.43%	28.57%			36.36%	54.55%	9.09%		
PE before LAG (ml/day)	≤ 500	10	1	6.945	0.031	10	2	1	11.523	0.021
		90.91%	9.09%			76.92%	15.38%	7.69%		
	500-1000	5	6			5	4	5		
		45.45%	54.55%			35.71%	28.57%	35.71%		
	≥ 1000	5	7			2	5	7		
		41.67%	58.33%			14.29%	35.71%	50.00%		

Abbreviation: NA, not applicable; M, Male; F, Female; PE, pleural effusion; LAG, lymphangiography; TGL, thoracic duct ligation during esophagectomy or before LAG; PE change, PE amount change before and after LAG; Clinical outcomes, the patients were healed LAG alone, LAG followed by minimal invasive procedure such as pleurodesis, or were needed a reoperation.

the great pressure at the leakage site which resulted from the ligation of thoracic duct during operation.

Currently, there is dispute about prophylactic ligation of the thoracic duct during esophagectomy. A recent meta-analysis was performed to compare the prevalence of chylothorax incidence in patients with prophylactic thoracic duct ligation (PLG) to non-prophylactic thoracic duct ligation (NPLG) during esophagectomy and found that there is no significant difference of the chylothorax incidence in PLG and NPLG groups (0.96% vs. 1.51%, $P = 0.05$) [29]. In addition, thoracic duct, an important part in digestive system, plays import role in enteral nutrition absorption after operation and prophylactic thoracic duct ligation will affect the nutritional status of the patients [30]. So the ligation of thoracic duct is not recommended especially when the tumor does not approach the thoracic duct. Lipiodol LAG can serve as a minimally invasive therapy method when chylous leakage occurs after esophagectomy. Further, we performed a systematical literature review to summarize the use of lipiodol LAG in management of the chylous leakage after esophagectomy and to verify our speculations.

Combined with our study, a total of 42 cases were identified (Table 1). Consistent with our speculation, patients with preservation of thoracic duct were more likely cured by LAG alone or LAG followed by minimal invasive treatment while the patients with thoracic duct ligation needed more reoperation after LAG, suggesting that preservation of thoracic duct was a favorable factor for the outcomes of chylous leakage after LAG. Similar to the previous reports, we also found that the PE amount after lymphangiography was a helpful diagnostic measure for the prediction of healing after lymphangiography.

Conclusions

Due to the function of thoracic duct in enteral nutrition absorption and extremely low incidence of chylous leakage after esophagectomy, prophylactic thoracic duct ligation should not be performed especially when the tumor does not approach the thoracic duct that will help to avoid excessive operation and post-operative recovery. Lipiodol LAG can be used as a minimally invasive therapy method when chylous leakage occurs after esophagectomy.

Acknowledgements

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Disclosure of conflict of interest

None.

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