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 e 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-
Lymphangiography and chylous leakage after esophagectomy

tive, a second surgery is often required to ligate
the thoracic duct [11]. However, surgical treat-
ment 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 treat-
ments and outcomes of refractory chylous
leakage after esophagectomy in our center in
recent 10 years and combined a systematic lit-
erature review to investigate the therapeutic
effects of LAG in management of post-esopha-
gectomy chylous leakage.

Patients and methods

Patients

A retrospective analysis of 1198 patients with
esophageal cancer undergoing esophagecto-
my from 2007 to 2017 in our hospital, Beijing
Cancer Hospital & Institute, Beijing, China, was
performed. The patients with post-esophage-
tomy 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 inter-
ventional radiologists. Briefly, 1.5 ml of a mix-
ture consisting of methylene blue and 2% lido-
caine (1:1) was injected subcutaneously be-
 tween 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 ex-
posed 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 ob-
tained to observe lymphatic channels and chy-
lous leakage.

Systematic literature search

To summarize the lymphangiography manage-
ment 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 accord-
ing to PRISMA guidelines. The following search-
ning key words were used: “chylothorax OR chyle
OR chylous leakage”, “lymphangiography”, and
“esophageal cancer OR esophagectomy”. In-
clusion 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 pub-
lished 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 sep-
parated; (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 infor-
mation including thoracic duct was resected or
not, amount of pleural effusion before and after
conventional treatment, conservative treatme-
nt strategy, amount of pleural effusion before
lymphangiography, the interval between esoph-
agectomy and lymphangiography, pleural effu-
sion after lymphangiography, and additional
treatment and outcomes at follow up were col-
lected. Chi-square test and Fisher’s exact test
were used to determine the associations of dif-
ferent characteristics with clinical outcomes of
the patients with post-esophagectomy chylous
leakage undergoing LAG.

Results

Patients

From 2007 to 2017, 1198 patients with esopha-
geal 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 con-
servative 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 therapeu-
ctic effectiveness of lymphangiography on
post-esophagectomy chylous leakage, we re-
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 difficulty 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. Therefore, 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 cT1NOM0, 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 somatostain was administrated 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 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 performed further 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 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 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. 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Discussion

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

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
Lymphangiography and chylous leakage after esophagectomy

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Case</th>
<th>Age (yrs.)</th>
<th>Gender</th>
<th>Thoracic duct</th>
<th>PE before LAG (ml/day)</th>
<th>LAG date (POD)</th>
<th>PE after LAG (ml/day)</th>
<th>Additional treatments after LAG</th>
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<td>Resected</td>
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<td>21</td>
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<td>93</td>
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<td>Shimakawa et al, 2017</td>
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<td>Yannes et al, 2017</td>
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<td>NA</td>
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<td>963</td>
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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 surrounding 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...
Lymphangiography and chylous leakage after esophagectomy

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 procedure 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.

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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>PE change</th>
<th></th>
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<th></th>
<th>Clinical outcomes</th>
<th>Chi-square</th>
<th>P-value</th>
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<tr>
<td></td>
<td>≥ 50%</td>
<td>&lt; 50%</td>
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<td></td>
<td>Healed</td>
<td>Minimal invasive procedure</td>
<td>Reoperation</td>
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<tr>
<td>Age</td>
<td>&lt; 65 yrs</td>
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<td>6</td>
<td>0.971</td>
<td>0.324</td>
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<td>5</td>
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<tr>
<td></td>
<td>≥ 65 yrs</td>
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<tr>
<td>Gender</td>
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<td>12</td>
<td>0.672</td>
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<td>11</td>
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<tr>
<td></td>
<td>71.43%</td>
<td>39.39%</td>
<td>27.27%</td>
<td>33.33%</td>
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<td>0.361</td>
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<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>71.43%</td>
<td>36.36%</td>
<td>54.55%</td>
<td>9.09%</td>
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<td>PE before LAG (ml/day)</td>
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<td>9</td>
<td>6.945</td>
<td>0.031</td>
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<tr>
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<td>15.38%</td>
<td>7.69%</td>
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<td>5</td>
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<td>45.45%</td>
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<td>28.57%</td>
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<td>41.67%</td>
<td>35.71%</td>
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</tbody>
</table>

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.
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Disclosure of conflict of interest

None.

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References


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