Survival Analysis of Patients with Thoracic Duct Ligation during Thoracoscopic Esophagectomy

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ABSTRACT

Objective: To determine the effect of thoracic duct ligation during thoracoscopic esophagectomy on esophageal cancer patients survival.

Study Design: A descriptive study.

Place and Duration of Study: Tai'an City Central Hospital, Tai'an, Shandong, China, from June, 2016 to June, 2021.

Methodology: All cT1b-3N0M0 stage esophageal cancer patients were randomly divided into thoracic duct ligation group and non-ligation group. In addition to thoracoscopic esophagectomy, thoracic duct ligation was also performed in the experimental group. The general data of two groups were compared by Chi-square test, with statistical significance at $p < 0.05$. The effect of thoracic duct ligation on disease-free survival (DFS) and overall survival (OS) was analysed by Kaplan-Meier and Cox regression.

Result: There was no significant difference in gender, age, tumor location, depth of invasion, degree of differentiation and presence of tumor thrombus between the ligation group (33 cases, 47.8%), and the non-ligation group (36 cases, 52.2%). Cox regression analysis showed that depth of invasion ($p = 0.0014$), degree of differentiation ($p = 0.0036$), presence of tumor thrombus ($p = 0.0367$) and thoracic duct ligation ($p = 0.0057$) were independent factors affecting DFS. Meanwhile, the depth of invasion ($p < 0.0001$), presence of tumor thrombus ($p = 0.0073$) and age ($p = 0.0129$) were independent factors affecting OS.

Conclusion: Thoracic duct ligation during thoracoscopic esophagectomy can affect DFS in patients with pT1b-3N0M0 esophageal squamous cell carcinoma, and the thoracic duct ligation, depth of invasion, degree of differentiation and presence of tumor thrombus are independent factors. Meanwhile, the depth of invasion, presence of tumor thrombus and age were independent factors affecting OS.

Key Words: Esophageal cancer, VATS, Esophagectomy, Thoracic duct ligation, DFS, OS.

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INTRODUCTION

The immunologists, honoured with the 2018 award in physiology or medicine, pioneered immunotherapy, which harnesses the body's immune system to fight cancer and achieved great success.^{1,2} There have been different opinions on whether to preventively ligate the thoracic duct during esophagectomy.³⁻⁵ With the development of medicine, video assisted thoracic surgery (VATS) has gradually become the mainstream surgical method for the treatment of early- and middle-stage of esophageal cancer due to its advantages of small trauma and rapid recovery.⁶

Under the new surgical method, there is still need to consider whether the thoracic duct should be ligated. Previous studies have shown that the prophylactic ligation of thoracic duct during thoracoscopic esophagectomy can affect the early post-operative absorption function and immune function, especially the decrease of CD4+ T cells.^{7,8} So whether the ligation of thoracic duct will cause serious damage to the immune system, thus affecting the OS and DFS is a subject worthy of study.

The aim of this study was to analyse the survival of patients undergoing thoracic duct ligation with esophageal cancer.

METHODOLOGY

Patients with esophageal cancer admitted to Tai'an City Central Hospital, Tai'an, Shandong, China, from June, 2016 to June, 2021. Squamous cell carcinoma patients with T1b-3 invasion, confirmed by endoscopic ultrasonography and biopsy, were enrolled. Patients with distant metastasis and lymph node metastasis detected by PET CT, those with serious cardiopulmonary and immune diseases, and postoperative pathology beyond T1b-3N0M0 stage, were excluded from the study. The general

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condition was evaluated by Doppler echocardiography, lung function, liver and kidney function, blood routine coagulation and so on. The study was approved by the Committee on Medical Ethics of the Hospital, and written informed consent was obtained from all patients.

All patients underwent thoracoscopic and laparoscopic esophagectomy with cervical mechanical anastomosis by the same group of thoracic surgeons. All diagnoses and treatments were carried out in strict accordance with NCCN Clinical Practice Guidelines in Oncology.⁹⁻¹² To identify thoracic duct easily, patients were advised to drink 100–150 ml olive oil 8–12h before operation.¹³ During operation, the azygos arch were ligated and cut off to make it easier to free the esophagus and clean the lymph nodes. Behind lower segment of esophagus, the thoracic duct can be recognised easily and separated between the descending aorta and the azygos vein. The patients were randomly assigned to the experimental group need to ligate the thoracic duct, after the thoracic esophagus was completely free. In order to minimise the influence of technique factors, a single gastroenterologist conducted gastroscopy and endoscopic ultrasound grading, and a single anesthesiologist performed intraoperative anesthesia and vital signs monitoring.

The studied variables included age (≥ 60 , <60), gender (male, female), T stage (T1b, T2, T3), differentiation (G1, G2, G3), tumor location (upper, middle, lower), thoracic duct ligation (yes or no), and vascular cancer embolus (yes or no). All patients were reexamined every three months in two years, every six months in five years and every year after five years.¹⁴ The follow-up deadline was June 16 2021. The follow-up examination item included blood routine, gastroscope, chest CT (plain scan or enhanced scan), neck and abdominal color Doppler ultrasound, etc. PET-CT, bone scan, MRI, etc. were supplemented according to the patients' symptoms, signs and routine examination. OS (status = 1 for death, 0 for censored) was measured from the date of operation to the date of death or last follow-up and censored at the last contact date in surviving patients. DFS (status = 1 for tumor recurrence or metastasis, 0 for censored) was measured from the date of operation to the date of first evidence of relapse or death as a result of any cause, which ever was observed first. For patients who had not relapsed or died, DFS was censored at the last date that the absence of relapse was confirmed.

Chi-square test was used to compare the differences for categorical variables. OS and DFS curves were calculated by the Kaplan-Meier method and compared by the unstratified log-rank test. A Cox regression model with stepwise selection was used for the multivariate analyses. Statistical significance was assumed for p-value of less than 0.05. All statistical analyses were performed using SAS 9.2 software.

RESULTS

After early screening, a total of 71 patients were enrolled in the group. In the ligation group, one case each of anastomotic leakage and severe pulmonary infection were excluded. No chylothorax occurred in both groups. Finally, 69 patients entered the study and completed the follow-up. There was no

significant difference in gender, age, tumor location, depth of invasion, degree of differentiation and presence of tumor thrombus between the thoracic duct ligation group (33 cases) and the non-ligation group (36 cases) ($p > 0.05$). The results are shown in Table I.

Table I: Comparison of clinical data between ligation group and control group.

Data	Classification	PLG (n,%)	NPLG (n,%)	p
Age	≥ 60	19(51.4)	18(48.6)	0.5285
	<60	14(43.7)	18(56.3)	
Gender	Male	28(49.1)	29(50.9)	0.6384
	Female	5(41.7)	7(58.3)	
Location	Up	5(45.5)	6(54.5)	0.6886
	Middle	18(52.9)	16(47.1)	
	Down	10(41.7)	14(58.3)	
Invasion depth	T1b	17(51.5)	16(48.5)	0.8319
	T2	10(45.5)	12(54.5)	
	T3	6(42.9)	8(57.1)	
Differentiation	G1	7(50.0)	7(50.0)	0.6832
	G2	17(43.6)	22(56.4)	
	G3	9(56.2)	7(43.8)	
Cancer thrombus	Yes	7(46.7)	8(53.3)	0.9191
	No	26(48.1)	28(51.9)	

PLG: Prophylactic thoracic duct ligation; NPLG: Non-prophylactic thoracic duct ligation.

Figure 1: Single factor analysis of the effect of T stage, tumor differentiation, thoracic duct ligation and vascular tumor thrombus on DFS.

DFS was calculated and plotted with the Kaplan-Meier method as shown in Table II and Figure 1. The results showed that gender, age and tumor location had no significant effect on DFS ($p > 0.05$), but depth of invasion, degree of differentiation, presence of tumor thrombus and thoracic duct ligation had significant effect on DFS ($p < 0.05$).

Cox proportional hazard models for DFS was built for those prognostic factors with $p < 0.1$ in the univariate analysis as shown in Table III-a. The result showed that invasion depth [HR=2.495, 95% CI (1.426, 4.366), $p=0.0014$], tumor differentiation [HR=2.964, 95% CI (1.426, 6.158), $p=0.0036$], vascular cancer embolus [HR=3.385, 95% CI (1.078, 10.626), $p=0.0367$], and thoracic duct ligation [HR=4.088, 95% CI (1.506, 11.099),

$p=0.0057$] were the independent risk factors affecting the DFS.

OS was calculated and plotted with the Kaplan-Meier method as were shown in Table II and Figure 2. The results showed that gender, age, tumor location, degree of differentiation ($p = 0.06$) and thoracic duct ligation had no significant effect on OS ($p > 0.05$), but depth of invasion and presence of cancer embolus had significant effect on OS ($p < 0.05$).

Table II: Single factor analysis of the influence of clinical and pathological factors on DFS and OS.

Data	Classification	N (%)	DFS p-value	OS p-value
Gender	Male	57(82.6)	0.9785	0.9797
	Female	12(17.4)		
Age	≥ 60	39(56.5)	0.8180	0.3687
	< 60	30(43.5)		
Location	Upper	11(16.0)	0.4034	0.7202
	Middle	35(50.7)		
	Lower	23(33.3)		
Invasion depth	T1b	33(47.8)	0.0135	< 0.0001
	T2	22(31.9)		
	T3	14(20.3)		
Differentiation	G1	14(20.3)	0.0204	0.0600
	G2	39(56.5)		
	G3	16(23.2)		
Cancer thrombus	Yes	15(21.7)	0.0020	0.0055
	No	54(78.3)		
Thoracic duct ligation	Yes	33(47.8)	0.0325	0.7085
	No	36(52.2)

Figure 2: Single factor analysis of the effect of T stage, tumor differentiation, thoracic duct ligation and vascular tumor thrombus on OS.

Cox proportional hazard models for OS was built for those prognostic factors with $p < 0.1$ in the univariate analysis as shown in Table III-b. The result show that age [HR=0.895, 95% CI (0.819, 0.977), $p = 0.0129$], invasion depth [HR=21.968, 95% CI (5.366, 89.29), $p < 0.0001$], vascular cancer embolus [HR=7.183, 95% CI (1.700, 30.351), $p=0.0073$] were the independent risk factors

affecting the OS.

DISCUSSION

Thoracic duct ligation is an effective method for the treatment of chylothorax, but there are academic disagreements on whether preventive ligation can prevent chylothorax.^{3-5,15} With the development of medicine, people are paying more and more attention to the unlimited potential of immune system in tumor treatment. Previous studies confirmed that preventive thoracic duct ligation had a bad effect on patients, especially the inhibition of postoperative immune function.^{7,8} This time, a long-term follow-up of the patients was conducted to detect early metastasis and calculate survival time.

According to the guidelines, for intramucosal esophageal cancer (T1a), endoscopic rather than thoracoscopic resection is generally chosen.⁹⁻¹² At the same time, the patients beyond T3N0M0 who often need chemoradiotherapy and then have interference factors on OS and DFS, therefore, T1b-3N0M0 patients were selected as the subjects.⁹⁻¹²

Some early scholars proposed that in the traditional thoracotomy esophagectomy, preventive thoracic duct ligation will not affect the immune function of patients, so it will¹³⁻¹⁵ not have a significant impact on the long-term survival of patients. Unlike left side transthoracic esophagectomy, thoracoscopic esophagectomy is usually performed through the right chest, and the azygos vein arch usually needs to be ligated and cut off for easier to free esophagus and clean lymph node.¹⁶ There are a number of communicating branches between azygos vein and thoracic duct.¹⁷ Most of the lymph in the whole body flows back to the blood through the thoracic duct or the collateral circulation between the thoracic duct and the azygos vein. When the thoracic duct and azygos arch are transected at the same time, lymph fluid and a large number of lymphocytes in it are difficult to return to the blood in a short time. It can be imagined that the decrease of immune function after operation might give the residual tumor cells an opportunity to escape and metastasize.¹⁸ In this study, postoperative follow-up also confirmed this result. Cox regression analysis showed that preventive thoracic duct ligation had a significant impact on DFS and was a high-risk factor for postoperative metastasis. The results of this study are the same as those of Fei,¹⁹ thoracic duct ligation did not affect the OS significantly, but it was an independent risk factor affecting DFS.

In the study of the effect of age on long-term survival, the results of univariate analysis and multivariate analysis were different. The authors analysed the reasons as follows: In the Kaplan-Meier analysis of OS, 60 years was taken as the boundary and changed into a binary variable. The result showed that age ($p = 0.3687$) had no significant effect on OS. In the Cox regression analysis of OS, the age ($p = 0.0129$) was a continuous variable and entered the regression model and became independent risk factors of OS.

Table III-a: Cox regression multivariate analysis results of DFS.

DATA	β	SE	Wald x2	p	HR (95%CI)
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Invasion depth	0.91445	0.28545	10.2627	0.0014	2.495 (1.426, 4.366)
Differentiation	1.08642	0.37315	8.4768	0.0036	2.964 (1.426, 6.158)
Cancer embolus	1.21929	0.58371	4.3633	0.0367	3.385 (1.078, 10.626)
Thoracic duct ligation	1.40811	0.50959	7.6353	0.0057	4.088 (1.506, 11.099)

Table III-b: Cox regression multivariate analysis results of OS.

DATA p	β	SE	Wald x2	p	H (95%CI)
Age	-0.11148	0.04484	6.1817	0.0129	0.895 (0.819, 0.977)
Invasion depth	3.08957	0.71910	18.4591	<0.0001	21.968 (5.366, 89.926)
Cancer embolus	1.97169	0.73529	7.1905	0.0073	7.183 (1.700, 30.351)

Although in Qiu's study, age as a hierarchical variable also obtained the same results, the present authors believe that in Cox regression analysis, age is more accurately calculated as a continuous variable.²⁰

CONCLUSION

Thoracic duct ligation can affect the DFS after thoracoscopic esophagectomy in esophageal squamous cell carcinoma patients with pT1b-3N0M0 stage. The thoracic duct ligation, depth of invasion, degree of differentiation and presence of tumor thrombus are independent factors affecting DFS; meanwhile the depth of invasion, presence of cancer embolus and age were independent factors affecting OS.

ETHICAL APPROVAL:

The study was approved by the Committee on Medical Ethics of the Hospital.

PATIENTS' CONSENT:

Written informed consents were obtained from all patients.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

RY: Experimental design, ethical application defence, main surgery, statistical analysis, article writing.

SS: Preoperative and postoperative gastroscopy, biopsy, ultrasonic endoscopy.

LY: Experimental design, article writing.

HL: Intraoperative anesthesia, postoperative monitoring.

RZ: Operation, personnel coordination, postoperative follow-up.

PW: Funds management, participation in surgery, postoperative management.

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