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Efficacy of Lauromacrogol Injection for Ablation of Benign Predominantly Cystic Thyroid Nodules and Related Factors: A Prospective Study

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Objective: To prospectively evaluate the efficacy of lauromacrogol injection for ablation (LIA) of benign predominantly cystic thyroid nodules and its related factors.

Materials and Methods: A total of 142 benign predominantly cystic thyroid nodules (median volume, 12.5 mL; range, 0.4–156 mL) in 137 patients (male:female sex ratio, 36:101; mean age ± standard deviation [SD], 49 ± 13 years) were treated with LIA after being confirmed as benign via cytology. The volume reduction rate (VRR) of the nodules and cosmetic score were evaluated during follow-up at 1, 3, and 6 months after treatment and every 6 months thereafter. A VRR of ≥ 50% at the 12-month follow-up was considered to indicate effective treatment. The associations between the clinical factors and nodular ultrasound features, including the initial nodule volume, proportion of solid components, vascularity grade and ineffective treatment (VRR of < 50% at the 12-month follow-up), and regrowth were analyzed.

Results: All patients completed follow-up for at least 12 months. The average ± SD follow-up period was 32 ± 11 months (range, 12–54 months). The effective treatment rate was 73.2% (104/142), while the regrowth rate was 12.0% (17/142) at the last follow-up. Grade 2–3 intranodular vascularity in the solid components of the nodules was the only independent factor associated with ineffective treatment, with an odds ratio (reference category, grade 0–1) of 3.054 (95% confidence interval, 1.148–8.127) (p = 0.025).

Conclusion: LIA is an effective treatment for predominantly cystic thyroid nodules. Grade 2–3 intranodular vascularity in the solid components of nodules is the only independent risk factor for ineffective LIA.

Keywords: *Ablation; Predominantly cystic nodule; Lauromacrogol; Thyroid; Ultrasound*

INTRODUCTION

Benign cystic thyroid nodules are a very common thyroid problem in the clinical setting. Image-guided minimally invasive treatment is recommended for patients with "symptomatic" benign cystic nodules [1-4]. Ultrasound-guided percutaneous ethanol ablation (EA) is the most commonly used chemical ablation method for treating cystic thyroid nodules [5,6]. However, owing to China's restrictions on the use of anhydrous alcohol in humans, EA is not widely practiced in China.

Lauromacrogol (polyoxyethylene lauryl ether) is a sclerosing agent with a local anesthetic effect, which can react on vascular endothelial cells and epithelial cells on cystic walls to induce aseptic inflammation and fibrosis [2,7,8]. It has been reported that the use of lauromacrogol yielded good results in the treatment of esophageal and gastric varices and benign cystic lesions in substantial organs, such as the liver, kidney, and pancreas [9-13]. Therefore, many clinicians have started exploring the use of lauromacrogol as an alternative to ethanol in the treatment of benign cystic thyroid nodules in China.

Cystic thyroid nodules include cystic (> 90% fluid components) and predominantly cystic nodules (51%–90%

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fluid components) [3]. Kim et al. [14] and Suh et al. [15] believed that the treatment effect of EA in cystic thyroid nodules was better than that in predominantly cystic thyroid nodules [2,14,15]. Furthermore, the efficacy of EA was related to the ultrasound features of the nodules [2,14,15]. A previous study has also found that the success rate of lauromacrogol injection for ablation (LIA) in cystic nodules was better than that in predominantly cystic nodules (91.7% vs. 75.9%) [16]. However, the factors related to the treatment effect of LIA in predominantly cystic thyroid nodules have not been identified.

The purpose of this study was to investigate the efficacy of LIA in the treatment of predominantly cystic thyroid nodules and the factors related to the therapeutic effect.

MATERIALS AND METHODS

Study Design

This prospective study was approved by our Institutional Ethics Committee (protocol number: KY2017-125). All patients provided informed consent after fully understanding the treatment plan and risks prior to LIA. The study included patients with thyroid nodules who visited our outpatient department from July 29, 2016 to June 26, 2019. Patients treated from 2016 to 2018 have been included in our previous study on the efficacy of LIA [16]. The inclusion criteria were as follows: 1) predominantly cystic nodules with 50%–90% cystic components based on ultrasonic assessments, 2) nodules causing aesthetic problems or compression symptoms, 3) benignity confirmed via at least one ultrasound-guided fine needle aspiration cytology, and 4) normal thyroid function. Meanwhile, the exclusion criteria were as follows: 1) malignant tumors or follicular neoplasms confirmed via cytology, 2) non-cooperation on puncture therapy, 3) abnormal coagulation function, 4) pregnancy, and 5) loss to follow-up within 12 months.

Patients

A total of 253 nodules in 241 consecutive outpatients in our department were treated with LIA (Fig. 1). Twenty-five predominantly cystic nodules in patients who were lost to follow-up and 86 cystic nodules were excluded. Finally, 142 predominantly cystic nodules in 137 patients were included in this study.

Ultrasound and Ultrasound-Guided LIA

The patients' age, sex, initial nodule volume, and basic information were recorded. Before treatment, a routine physical examination of the neck was performed by the radiologist to evaluate the cosmetic score (score 1: no enlargement or mass observed, score 2: palpable mass but not visualized, score 3: visible mass when swallowing, and score 4: obvious swelling and visible mass observed with the naked eye).

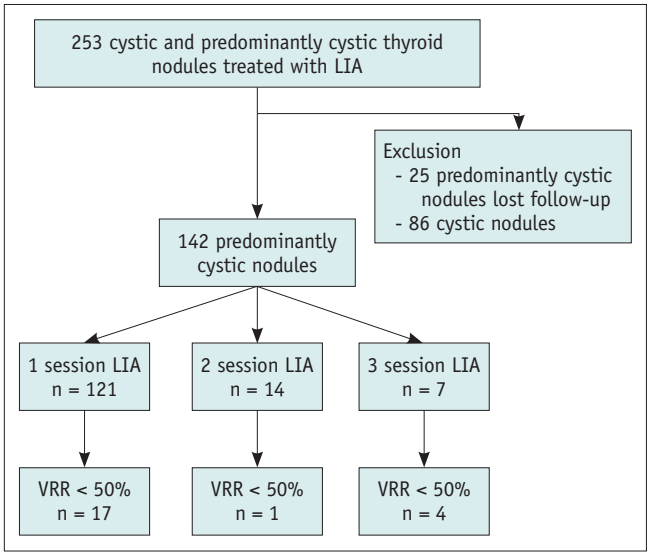

Fig. 1. Outcomes of 253 thyroid nodules treated with ultrasound-guided lauromacrogol ablation. LIA = lauromacrogol injection for ablation, VRR = volume reduction rate

The Resona 7 ultrasound device from Mindray Medical International in Shenzhen, China was used in this study. Using a high-frequency probe of L14-5 or L11-3, we adjusted the instrument to the best display mode. All imaging data were stored in the hard disc and DICOM system during treatment and follow-up. The location and size of the target nodules were recorded and measured in situ. The nodule volume was calculated using the following equation: $V = \pi abc/6$, where V refers to the volume; a, largest diameter in the longitudinal axis; and b and c, other two diameters in the transverse axis. On gray-scale ultrasound, the nodules were divided into two groups according to the proportion of the solid components (< 25% and ≥ 25%). Based on the vascularity of the solid components of the nodules, which was evaluated using color Doppler, the nodules were divided into four categories: grade 0, no vascularity; grade 1, peripheral vascularity only; grade 2, intranodular vascularity of < 50%; and grade 3, intranodular vascularity of ≥ 50% [14].

All the procedures were performed by three radiologists with over 10 years of experience in imaging and

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interventional ultrasound. No local anesthesia was administered during LIA. An 18–22-G needle connected to a three-way stopcock and a 25-mL syringe was used to extract fluid under ultrasound guidance (long axis of the ultrasound probe parallel to the needle) via the trans-isthmic approach. During this process, the fluid properties, including the color, viscosity, and volume of the fluid extracted, were recorded. Cyst fluid was extracted as much as possible. For nodules with viscous fluid that could not be easily aspirated, lavage and dilution were performed using 0.9% saline in the cavity. Finally, lauromacrogol solution (100 mg/10 mL, Tianyu Pharmaceutical Company) was slowly injected to the cystic cavity and retained there. When grade 2–3 vascularity was detected in the solid component of the nodules, local drug injection was performed simultaneously on the solid part in an attempt to disrupt the blood supply in the solid component. Generally, the volume of the injected lauromacrogol corresponded to 30%–50% of the volume of the fluid extracted. When 30%–50% of the extracted fluid volume exceeded 20 mL, the maximum amount of lauromacrogol retained in the cavity for a single session was 20 mL to reduce possible side effects, such as neck discomfort caused by drug leakage. After the procedure, the needle was withdrawn, but with no drug aspirated. The patients were then observed in the outpatient department for at least half an hour. They were allowed to leave the hospital after re-examination with ultrasound to ensure that there was no hematoma, drug leakage causing swelling, or dyspnea. Changes in the size and volume of the nodules as well as discomfort and complications during treatment were also recorded.

Follow-Up and Assessments

The follow-up period in all patients was more than 12 months (range, 12–54 months; average, 32 ± 11 months). Thyroid ultrasound was conducted at 1, 3, 6, and 12 months after LIA and every 6 months thereafter. The ultrasound examination was performed by two of the three radiologists in charge of LIA. In addition, the largest diameters, internal structure, and vascularity of the nodules were recorded. Changes in the volume reduction rate (VRR) after treatment were the main parameter assessed. The following equation was used: VRR = (initial volume-volume on the day of follow-up)/initial volume x 100%. The cosmetic score was recorded at the last follow-up at the end of the study. VRRs of ≥ 50% and < 50% at the 12-month follow-up were considered to indicate effective and ineffective treatments, respectively. Nodule regrowth was defined as an up to 50% increase in the nodule volume compared with the minimum recorded volume during follow-up [3,17]. Among the patients with regrowth, ineffective treatment, or effective treatment but with persistent cosmetic problem or compression symptom 3 months after LIA, further treatments were needed; they were recommended to undergo repeated LIA, radiofrequency ablation, or surgical treatment according to their wishes.

Statistical Analysis

Statistical analysis was conducted using SPSS version 16.0 (SPSS Inc.). A paired sample *t* test was used to compare the changes in the nodule volume and cosmetic score before and after LIA (at the last follow-up). The chi-square test was used to analyze the factors associated with ineffective treatment and regrowth rate, including age (< 45 vs. ≥ 45 years), initial volume (> 10 vs. ≤ 10 mL) [14], cosmetic score (> 3 vs. ≤ 3) [18,19], proportion of solid components (≥ 25% vs. < 25%), vascularity in the solid component (grade 0–1 vs. grade 2–3), and nature of the fluid (viscous vs. watery). Multiple logistic regression (enter

Table 1. Basic Information of Patients with 142 Predominantly Cystic Nodules in 137 Patients Treated with Lauromacrogol Injection of Ablation

Age, mean ± SD, year	49 ± 13
Sex, patient number	
Male:female	36:101
Solid components	
< 25%	89 (62.7)
25%–50%	53 (37.3)
Vascularity	
Grade 2–3	67 (47.2)
Grade 0–1	75 (52.8)
Watery	123 (86.6)
Viscous	19 (13.4)
Volume of remaining lauromacrogol, mean ± SD (range), mL	7.2 ± 7.0 (0.1–20)
Follow-up period, mean ± SD (range), month	32 ± 11 (12–54)
Cosmetic grade, mean ± SD	
Initial	3.3 ± 0.8
Last follow-up	1.5 ± 0.9
Volume, median (range), mL	
Initial	12.5 (0.38–156)
Last follow-up	1.0 (0.01–23.5)

Data are number of nodules with percentage in parentheses, unless specified otherwise. SD = standard deviation

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method) was then used to identify the independent factors associated with ineffective treatment. A p value of < 0.05 was considered statistically significant.

RESULTS

The clinical information of the 137 patients, including age, sex, and ultrasound features of the nodules, is listed in Table 1. There were significant differences in the changes in the nodule volume and cosmetic score before and after LIA (p < 0.001). The maximum amount of lauromacrogol retained in a single session was 20 mL, while that in multiple sessions was 60 mL.

In this study, 85.2% (121/142) of the nodules were subjected to one session of LIA; 9.9% (14/142), two sessions; and 4.9% (7/142), three sessions (Fig. 1). Among the 21 patients who received two to three sessions, effective treatment was achieved in 16 patients (76.2%). At the end of the study, 14 of the 22 patients with ineffective LIA underwent radiofrequency ablation, and eight patients were still being followed up.

The mean nodule volume changes in all 142 nodules before and 1, 3, 6, and 12 months after treatment are shown in Table 2. There was a significant decrease in the nodule volume between each follow-up within 6 months after treatment (all p < 0.05); however, there was no significant change observed after 6 months (p = 0.182). The average VRR (mean ± standard deviation) at 1, 3, 6, and 12 months after treatment was 56.7% ± 36.9%, 67.1% ± 32.8%, 72.2% ± 30.6%, and 73.1% ± 33.8%, respectively (Table 2). The average VRR at the last follow-up was 77.1% ± 29.7%.

Among the 28 patients with ineffective treatment at the

Table 2. Average Volume Changes in 142 Nodules during 12 Months Follow-Up

Time	Volume, mL	*P*	VRR*, %	VRR < 50%	VRR ≥ 50%
Initial	18.4 ± 20.6				
1 month	7.9 ± 16.8	0.000	56.7 ± 36.9	46 (32.4)	96 (67.6)
3 months	5.6 ± 11.2	0.000	67.0 ± 32.8	39 (27.5)	103 (72.5)
6 months	3.9 ± 6.5	0.032	72.2 ± 30.6	30 (21.1)	112 (78.9)
12 months	3.6 ± 6.3	0.182	73.1 ± 33.8	28 (19.7)	114 (80.3)

Data are mean ± standard deviation or number of nodules (percentage). p value: the comparison of the current measured volume with the previous measured volume. *The VRR was calculated for each follow-up using the initial volume as the basis. VRR = volume reduction rate

Table 3. Univariable Analysis of Factors Related to VRR < 50% at 1 Year Follow-Up of Lauromacrogol Ablation in 142 Nodules

Variables	VRR < 50% n = 28	VRR ≥ 50% n = 114	Total n = 142	*P* (2-Sided)
Age, years				0.051
≤ 45	16 (29.1)	39 (70.9)	55	
> 45	12 (13.8)	75 (86.2)	87	
Cosmetic score				0.088
> 3	8 (12.7)	55 (87.3)	63	
≤ 3	20 (25.3)	59 (74.7)	79	
Initial volume, mL				0.011
≤ 10	18 (30.0)	42 (70.0)	60	
> 10	10 (12.2)	72 (87.8)	82	
Proportion of solid components				0.005
< 25%	11 (12.4)	78 (87.6)	89	
25%–50%	17 (32.1)	36 (67.9)	53	
Vascularity				0.006
Grade 0–1	8 (10.7)	67 (89.3)	75	
Grade 2–3	20 (29.9)	47 (70.1)	67	
Nature of internal fluid				0.766*
Watery	25 (20.3)	98 (79.7)	123	
Viscous	3 (15.8)	16 (84.2)	19	

Data are number of nodules (percentage). *Fisher's exact test. VRR = volume reduction rate

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12-month follow-up, 60.7% (17/28) had a proportion of solid components of 25%–50%, and 71.4% (20/28) had a vascularity grade of 2–3 in the solid components (Table 3). There were no significant differences in age, the cosmetic score before treatment, and the cyst fluid property (viscous/watery) between the patients with VRRs of ≥ 50% and < 50% at the 12-month follow-up. However, there were significant differences in the initial nodule volume (p = 0.011), proportion of solid components (p = 0.005), and vascularity grade (p = 0.006) between those with VRRs of ≥ 50% and < 50% (Table 3, Figs 2, 3). The multiple logistic regression analysis showed that grade 2–3 vascularity in the solid components was the only independent factor associated with a VRR of < 50% at the 12-month follow-up (p = 0.025), with an odds ratio of 3.054 (95% confidence interval, 1.148–8.127) (Table 4).

Of the 142 nodules that were followed up for at least 12 months, 17 nodules showed regrowth at 3–18 months. There were no significant differences in age and the initial nodule volume, cosmetic score, proportion of solid components, vascularity grade in the solid components, and fluid property between the patients with and without nodule regrowth (Table 5). Eight patients with nodule regrowth received two sessions of LIA and achieved a VRR of ≥ 50%. One patient with nodule regrowth received three sessions of LIA and achieved a VRR of 95.2%. One patient with nodule regrowth underwent surgery and was pathologically diagnosed with nodular goiter. At the end of the study, seven patients were still under observation.

Five patients had mild fever, and one patient had

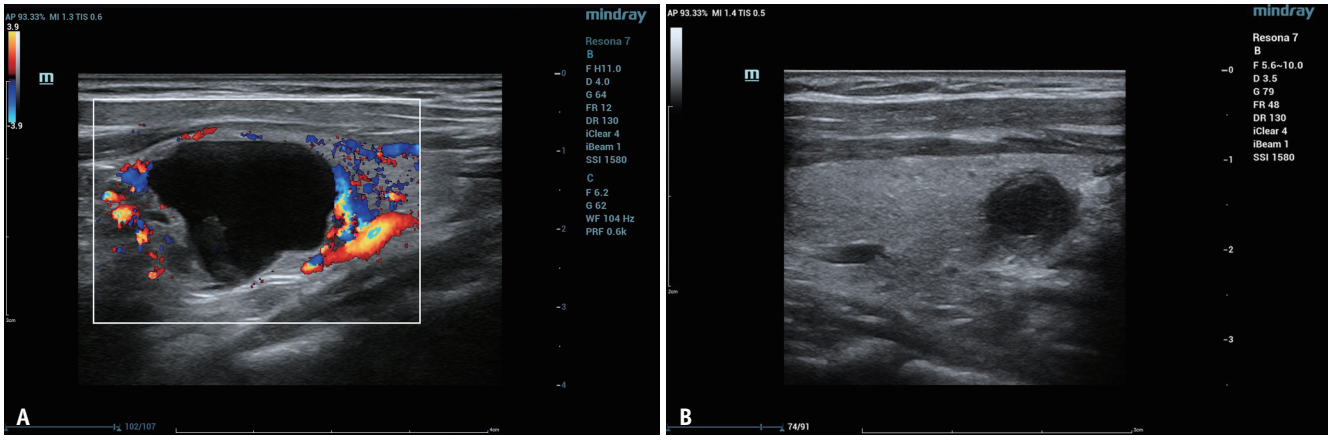

Fig. 2. Successful case: ultrasonographic image of a 62-year-old male patient with a thyroid nodule (Bethesda II cytology; initial volume, 6.21 mL before lauromacrogol injection for ablation).
A. A predominantly cystic nodule with grade 1 vascularity in the solid component. **B.** At 18 months after lauromacrogol ablation, the volume decreased to 0.28 mL (volume reduction rate, 95.5%).

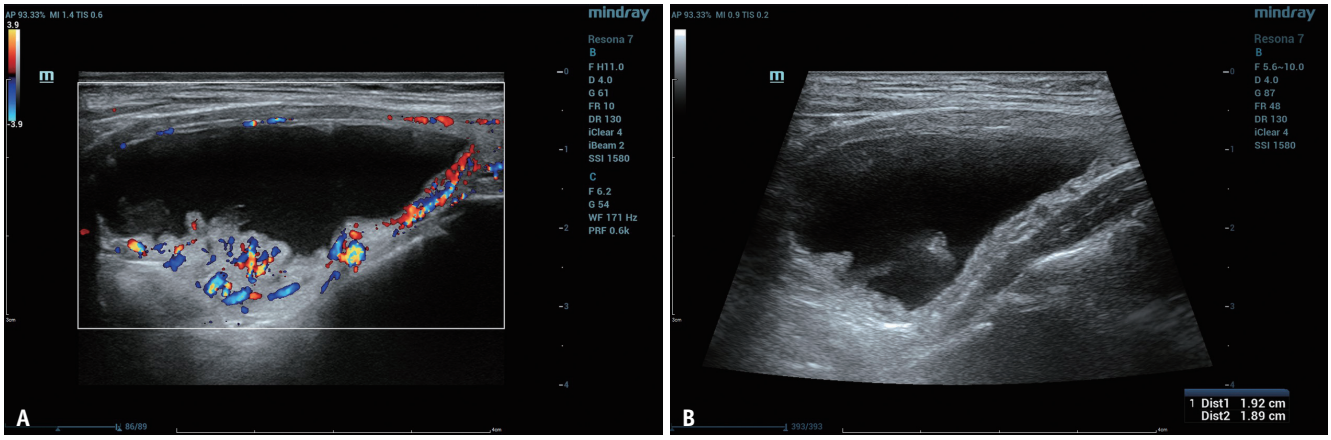

Fig. 3. Failed case: ultrasonographic image of a 38-year-old female patient with a thyroid nodule (Bethesda II cytology; initial volume, 5.5 mL before treatment).
A. A predominantly cystic nodule with grade 3 vascularity in the solid part. **B.** At the 6-month follow-up after three sessions of lauromacrogol injection for ablation, the volume increased to 7.99 mL. This patient finally underwent ultrasound-guided radiofrequency ablation.

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moderate pain after LIA. However, these symptoms disappeared within 1 week. Severe complications were not observed in this study.

Table 4. Multiple Logistic Regression Analysis of Factors associated with Volume Reduction Rate < 50% at 1 Year Follow-Up

Variables	OR	95% CI for OR		*P*
		Lower	Upper	
Vascularity				
Grade 0–1 (reference)				
Grade 2–3	3.054	1.148	8.127	0.025
Proportion of solid components				
< 25% (reference)				
25%–50%	2.400	0.951	6.056	0.064
Sex				
Female (reference)				
Male	0.661	0.208	2.108	0.485
Age, years				
> 45 (reference)				
≤ 45	2.113	0.835	5.347	0.114
Initial volume, mL				
≤ 10 (reference)				
> 10	0.305	0.078	1.192	0.088
Cosmetic score				
≤ 3 (reference)				
> 3	1.330	0.319	5.539	0.695

CI = confidence interval, OR = Odds ratio

DISCUSSION

It has been reported that the success rate of EA was 85.0%–98.5% in the treatment of cystic thyroid nodules and only 64.0%–73.2% in the treatment of predominantly cystic nodules [2,20-28]. In the study by Jang et al. [22], 33.0% of predominantly cystic nodules were ineffectively treated with EA. In this study, 19.7% (28/142) of the predominantly cystic nodules were ineffectively treated (VRR of < 50%) at the 12-month follow-up after LIA.

Previous studies have shown that the initial nodule volume, blood supply in the solid components, and proportion of solid components all affected the results of chemical ablation [2,29]. Studies have also suggested that the initial volume of predominantly cystic nodules and blood supply in the solid components were independent risk factors for ineffective EA [2,14]. The efficacy of EA was better for nodules with a smaller volume and less blood supply in the solid components before treatment than for those with a larger initial volume (> 20 or > 10 mL) and rich blood supply [2,14,15]. According to Jang et al. [22], the proportion of solid components in nodules was the only factor affecting the results of a single session of EA. Although the initial nodule volume, proportion of solid components, and blood supply in the solid components of nodules were the factors associated with ineffective

Table 5. Univariable Analysis of Factors Related to the Regrowth of Lauromacrogol Ablation

Variables	Regrowth n = 17	Non-Regrowth n = 125	Total n = 142	*P* (2-Sided)
Age, years				0.599
≤ 45	8 (14.3)	48 (85.7)	56	
> 45	9 (10.5)	77 (89.5)	86	
Cosmetic score				1.000
> 3	8 (12.7)	55 (87.3)	63	
≤ 3	9 (11.4)	70 (88.6)	79	
Initial volume, mL				0.795
≤ 10	8 (13.3)	52 (86.7)	60	
> 10	9 (11.0)	73 (89.0)	82	
Proportion of solid components				0.428
< 25%	9 (10.1)	80 (89.9)	89	
25%–50%	8 (15.1)	45 (84.9)	53	
Vascularity				0.438
Grade 0–1	7 (9.3)	68 (90.7)	75	
Grade 2–3	10 (14.9)	57 (85.1)	67	
Nature of internal fluid				0.470*
Watery	16 (13.0)	107 (87.0)	123	
Viscous	1 (5.3)	18 (94.7)	19	

Data are number of nodules (percentage). *Fisher's exact test.

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treatment, grade 2–3 vascularity in the solid components was the only independent risk factor in the logistic regression analysis in this study.

In our logistic regression analysis, it was found that the initial nodule volume did not influence the nodule shrinkage. This may be attributed to the fact that lauromacrogol was retained in the cavity, ensuring adequate contact between lauromacrogol and the cyst wall of the nodules of any size. The proportion of solid components also did not affect the treatment effect. However, the high blood supply status (grade 2–3 vascularity) of the solid components reduced the treatment effect; this is probably because lauromacrogol was unable to destroy the vascular system of the solid components with rich blood supply, so the epithelial cells of the nodules could receive sufficient nutrition to remain active and continue to secrete fluid.

The regrowth rate of the 142 nodules observed at the end of follow-up in this study was 12.0% (17/142). Eight of these nodules achieved a VRR of > 50% after two to three sessions of LIA. This result was better than that reported following EA in predominantly cystic nodules (regrowth rate, 26.0%–38.3%). However, we did not find any factors (nodal characteristics) associated with regrowth, which may have been attributed to the small sample size of this study.

Although 76.2% (16/21) of the patients benefited from repeated LIA (two to three sessions), we observed that three sessions of LIA did not markedly improve the treatment efficacy (4/7 cases). In some cases, the nodules may be resistant to lauromacrogol. Ultrasound-guided thermal ablation should be considered for cases with intractable cystic nodules [6,29,30]. Owing to the high cost and relative damage to the thyroid gland and surrounding tissues caused by thermal ablation, this method is not recommended as a first-line treatment for predominantly cystic thyroid nodules [29,30]. However, it could be used as a complementary treatment following the failure of LIA.

There were several limitations in this study. First, this study was a single-center study lacking results from multiple investigations. Second, we only evaluated the cosmetic score without symptom parameters. Third, the number of nodule regrowth cases was too small to evaluate the long-term effects of LIA. Fourth, cytology was performed only once instead of twice for many nodules, which may lead to false-negative results for some malignant follicular tumors, although this possibility is extremely low.

In conclusion, LIA is an effective minimally invasive treatment for benign predominantly cystic thyroid nodules and can be an alternative treatment to EA. Grade 2–3 vascularity in the solid components of nodules is an independent risk factor for ineffective LIA.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Yi Jie Dong, Jian Qiao Zhou. Data curation: Yi Jie Dong, Zhen Hua Liu. Formal analysis: Yi Jie Dong. Funding acquisition: Yi Jie Dong. Investigation: Yi Jie Dong. Methodology: Yi Jie Dong, Jian Qiao Zhou. Project administration: Wei Wei Zhan. Resources: Jian Qiao Zhou, Yi Jie Dong, Zhen Hua Liu. Software: Jian Qiao Zhou, Yi Jie Dong. Supervision: Wei Wei Zhan. Validation: Jian Qiao Zhou. Visualization: Yi Jie Dong. Writing—original draft: Yi Jie Dong. Writing—review & editing: Yi Jie Dong.

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