Recurrence and additional treatment of cystic thyroid nodules after ethanol ablation:
Validation of three proposed criteria

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Abstract

Purpose

We evaluated three criteria for determining the need for additional treatment of cystic thyroid nodules after their recurrence following ethanol ablation (EA).

Materials and Methods

One hundred and fifty-four patients (M:F = 30:124; mean age, 53.4; range, 23–79 years) with 154 thyroid nodules (49 cystic and 105 predominantly cystic nodules) who presented between January 2014 and August 2017 were enrolled. All patients underwent follow-up ultrasonography (US) 1 month after EA, and were divided into therapeutic success and failure groups. The patients were evaluated according to three previously suggested criteria for recommending additional treatment: (1) nodules with ≥1 ml remnant fluid, (2) volume reduction <50%, (3) demonstration of solid component with vascularity.

Results

Thyroid nodules treated by EA showed significant volume reduction (18.4±21.6 to 4.2±6.5 [1-month follow-up] to 1.9±3.3 ml [final follow-up], p<0.001) and improvement in clinical problems. Additional treatment was unnecessary in 81%, 70%, and 71% of patients deemed as needing it according to the previously suggested criteria 1, 2, and 3, respectively.
Conclusion

Additional treatment after EA should be decided according to the combination of clinical problems and US features. Understanding of this concept will be useful in planning for the further treatment strategy following US-guided EA.
Keywords

Thyroid nodules, Ethanol, Ablation, Recurrence
Introduction

Image-guided non-surgical procedures such as ethanol ablation (EA) have been proposed as effective and less invasive approaches for the management of cystic (pure cystic) or predominantly cystic (cystic component > 50%) thyroid nodules causing pressure symptoms or complaints of neck bulging [1,2]. The Korean Society of Thyroid Radiology (KSThR) proposed strong recommendation of EA as first-line treatment method for cystic and predominantly cystic nodules that are not treated with simple aspiration[3].

Previous studies showed that EA achieved volume reduction for cystic (85–95% of cases) and predominantly cystic nodules (60–90% of cases) [4]; however, even though EA is known to be effective for reducing the volume of cystic or predominantly cystic thyroid nodules in most cases, they sometimes recur, and additional treatment needs to be considered [5-8]. For example, KSThR suggest radiofrequency ablation (RFA) for the incomplete resolved symptoms or recurrence following EA[3]. Although additional treatment of recurrent cystic or predominantly cystic thyroid nodules is effective, there are different suggested criteria for defining recurrence and the need for additional treatment, and the decision can be challenging to make in daily practice [6,7,9]. According to previous studies, recurrence is usually decided at 1-month follow-up ultrasonography (US) after EA, and three different definitions of recurrence have been suggested as follows: (1) nodules containing ≥1 ml of cystic fluid [6], (2) a volume reduction ratio of <50% [7,9], and (3) a vascular solid component in treated nodules [2].

Thus, a reasonable definition of recurrence requiring further treatment is
important for effective additional treatment strategy. We therefore evaluated three previously suggested US-based criteria for defining recurrence requiring treatment after EA of cystic or predominantly cystic thyroid nodules.

Materials and Methods

Our institutional review board approved this retrospective study, and the requirement for informed consent was waived. Informed consent for US-guided procedures was obtained from all patients prior to each procedure.

Patients

A total of 253 consecutive patients who underwent EA for cystic neck lesions at our institution between January 2014 and August 2017 were enrolled in this study (Fig 1). The eligibility criteria were as follows: (1) cystic (pure cystic) or predominantly cystic (cystic component more than 50%) thyroid nodules; (2) pressure symptoms and/or cosmetic problems; (3) normal serum concentrations of thyroid hormones and thyrotropin; (4) benign cytological results; and (5) no suspicious malignant features on US examination such as microcalcification, nonparallel orientation, spiculated or microlobulated margin [10].

Ninety-nine patients were excluded: 32 because they were lost to follow-up and 67 because they were treated for non-thyroidal lesions, such as thyroglossal duct cyst or lymphatic malformation. Finally, 154 patients (M: F = 30:124; mean age ± standard deviation, 53.4 ± 12.8 years; range, 23–79 years) with 154 cystic or predominantly
cystic thyroid nodules were analyzed. We underwent all enrolled thyroid nodules US-guided fine-needle aspiration (FNA) (average 1.5 times, range 1~5 times) and got result of non-diagnostic (29.9%, n = 46) or benign (70.1%, n = 108). After reviewing US image and considering biopsy numbers, we assumed non-diagnostic result as benign since the non-diagnostic FNA results were due to pure cysts without solid component. All 154 patients underwent follow-up US1-month after EA, and they were divided into two groups according to the final results: therapeutic success according to US (volume reduction ≥50%) and therapeutic failure according to US (volume reduction <50% or patients who underwent additional treatment).

**Pre-ablation assessment**

Before undergoing EA, US-guided FNA, laboratory examinations, and symptoms were assessed by two experienced radiologists. The characteristics of each thyroid nodule, including size, solid component, and vascularity, were evaluated using an iU22 (Philips Healthcare, Bothell, WA) or EUB-7500 US unit (Hitachi Medical Systems, Tokyo, Japan) with a linear high-frequency probe (5–14 MHz). The three orthogonal diameters of each nodule were measured on US, and the nodule volume (V) was calculated using the equation $V = \frac{\pi abc}{6}$, where a is the largest diameter, and b and c are the two perpendicular diameters [11].

Nodule vascularity was graded as follows: grade 1, no vascularity; grade 2, peripheral vascularity only; grade 3, intranodular vascularity ≤50%; and grade 4, intranodular vascularity >50% [12,13].
Symptom score was calculated with a 10 cm visual analogue scale (range, 0–10). The cosmetic score was assessed as grade 1 indicating no palpable mass, grade 2 indicating no cosmetic problem but a palpable nodule, grade 3 indicating a cosmetic problem on swallowing only, and grade 4 indicating a readily detectable cosmetic problem [14,15].

Ethanol ablation

EA was conducted on an outpatient basis by two radiologists with >10 years of experience, as described in previous articles [12,16,17]. First, a 16 or 18G needle was inserted into the cystic area of the nodule under guidance from a transverse US view. The cystic component was maximally removed when the needle tip approached the center of the cyst, and internal debridement was irrigated with saline. A volume of 99% ethanol to about 50% of that of the aspirated fluid volume was then injected slowly into the cyst. The injected ethanol (average 8.3 ml, range 1 ~ 20 ml based on the aspirated fluid amount) and needle were removed around 2 minutes later. After the procedure, the patient stayed at the hospital for about 30 minutes and was then discharged unless an immediate adverse event was noted. Repeat EA was performed using the same procedure as the initial EA.

Follow-up

Follow-up US examinations were performed on the treated nodules at 1, 6, and 12 months, and then every 6–12 months thereafter [12]. Changes in the cystic portion,
vascularity, diameter, and volume were evaluated. The effect of the treatment was assessed by measuring the volume reduction ratio, and by assessing the improvement in symptoms and cosmetic problems. Therapeutic success was defined as a volume reduction >50% at the last follow-up [18]. If a further US examination result after the 1-month follow-up was unavailable for any reason (such as follow-up at another hospital or refusal to attend follow-up because of absence of symptoms), the patient’s status was checked with a telephone interview, and the procedure was considered as therapeutic success if the first follow-up at 1 month after EA showed a volume reduction ratio of >50%. Any adverse events during the follow-up period were also checked.

Volume reduction ratio (VRR) was defined as [19]

\[
VRR(\%) = \frac{Initial\ volume - Post\ treatment\ volume}{Initial\ volume} \times 100
\]

Recurrent thyroid nodules were defined according to three previously suggested criteria (Fig. 1): (1) nodules with a fluid component ≥1 ml [6], (2) shrinkage of ≤50% of the initial nodule volume [7,9], and (3) demonstration of a solid component with vascularity [2]. The final results were compared for recurrences defined according to each of the three definitions. Delayed recurrence was defined as no recurrence detected at the 1 month post-EAUS, but a newly developed cystic portion of the treated thyroid nodule showing during the later follow-up period [2].

Additional treatment was not performed on all nodules defined as a clinical therapeutic failure at 1-month follow-up US, with a conservative treatment strategy. We decided additional EA after 2-month follow-up to prevent avoidable additional treatment. Avoidable additional EA was defined as patients who achieved therapeutic success at
last follow-up without additional treatment.

When a patient requested additional treatment because of incompletely resolved nodule-related symptoms and/or cosmetic problems, additional treatment was performed. These patients were regarded as clinical therapeutic failure.

**Statistical analysis**

Statistical analyses were performed using SPSS for Windows (version 18.0; SPSS, Chicago, IL) and R version 3.4.2. To evaluate the efficacy of EA, a paired \( t \)-test was used to compare variables (changes in the largest diameter, volume, vascularity, and symptomatic and cosmetic scores) between pre-EA, 1-month follow-up, and last month follow-up examinations.

To evaluate the previously proposed criteria for recurrence after EA, the patient’s final results were divided into therapeutic success and therapeutic failure groups, and the US results were compared using the \( t \)-test. The level of significance was defined as \( p < 0.05 \).

**Results**

Total 135 (87.7%) patients achieved therapeutic success while 19 (12.3%) patients experienced therapeutic failure. Table 1 shows the pre-treatment characteristics and parameter changes during follow-up. At 1 month and last follow-up, the volumes of the treated nodules had decreased significantly \( (p < 0.0001) \), and the clinical problems of the patients had improved significantly \( (p < 0.0001) \).
When the three previously proposed criteria for defining recurrence requiring further treatment [2,6,7,9] were applied to our patient group, 32 patients would require further treatment according to criterion 1 (nodules with a fluid component ≥1 ml), 20 patients according to criterion 2 (shrinkage of <50%), and 45 patients according to criterion 3 (a solid component with vascularity). For these three groups, avoidable additional EA were 81.3% (26/32), 70.0% (14/20), and 77.8% (35/45), respectively, with the numbers achieving therapeutic success being significantly higher than those who showed therapeutic failure (therapeutic failure: 18.8% [6/32], p<0.001; 30.0% [6/20], p=0.013; 22.2% [10/45], p<0.001, respectively). (Table 2, Figure 2–4).

A characteristic finding was that almost half of the cases in the therapeutic failure group showed increased vascularity (47.4%, 9/19). Seven cases showed delayed recurrence, four of whom underwent additional treatment with radiofrequency ablation (RFA), and finally achieved therapeutic success defined as a volume reduction of >50% at 12 months after treatment [20]; their average volume reduction ratio was 80.2%. The other two patients who did not undergo additional treatment showed finally therapeutic success (VRR with 76.3% and 51.7% at 13th and 12th month follow up respectively), and one patient was clinically asymptomatic (VRR 28.2%).

The mean follow up period was 18.1 ± 13.4 months. Final follow up of 6 patients (3.9%) was 1 month while others underwent follow up more than 6 months. (6 months; 48 patients (31.2%), 12 months; 31 patients (20.1%), more than 12 months; 69 patients (44.8%)). Follow up period did not show statistically different between therapeutic success and failure group (18.4 ± 13.4, range 1~47 months vs. 16.1 ± 13.0, range 1~46 months, p=0.48). We tried telephone survey for 16 patients (10.4%)
who lost outpatient clinic follow up after the 1 month. Six of them who achieved therapeutic success on 1 month follow up were not able to undergo survey, so we categorized them as therapeutic success group. Among 10 patients who answered the telephone survey, 1 patient underwent re-treatment in other hospital and others didn’t have recurrent symptom. We categorized patient who underwent re-treatment as therapeutic failure group while others categorized as therapeutic success group.

There were no major adverse events such as voice change, infection, esophageal injury, or tracheal injury after EA or RFA.

Discussion

Our study demonstrated that EA achieved significant volume reduction and improvement of clinical problems. Moreover, there was no major complication after the EA. When we applied the three previously proposed criteria [2,6,7,9] to our patient group, additional treatment was avoidable in 81%, 70%, and 71% of patients according to the previously suggested criteria 1, 2, and 3, respectively. Therefore, additional treatment should be decided carefully according to the actual clinical problems and US features combined. Understanding of this concept will be useful for doctors who perform US-guided EA to help them minimize unnecessary additional procedures.

EA is well known as an effective treatment for cystic thyroid nodules [21]. However, important issues of concern are how to define recurrence and when to plan for further treatment. As previous studies suggested different criteria for recurrence and additional treatment planning [2,6,7,9], confusions may arise during follow-up in clinical practice. Previous articles recommended making decisions on additional
retreatment at 1 month follow-up according to US features such as the existence of >1 ml cystic fluid [6], a volume reduction ratio <50% [7,9], or a solid component with internal vascularity [2]. However, we found that just simple observation without additional treatment can achieve therapeutic success.

Previous studies revealed that EA reduces the volume of cystic thyroid nodules by 85–98.5% and the volume of predominantly cystic nodules by 64–73.2% [13]. It is suggested that the reason that cystic thyroid nodules typically show a greater volume reduction than benign solid nodules is that the solid components are more resistant to ethanol, and the vascularity of solid nodules drains the ethanol, thus limiting the success of the EA [22-24]. Furthermore, the solid component was found to be the only independent factor predicting volume reduction after a single session of EA [13]. In our study, we found that about 84.2% of nodules (16/19) in the therapeutic failure group showed increased vascularity, which is in agreement with a previous report [2]. Vascularity is also an important factor in therapeutic success after RFA or laser ablation [20,25-27]. Even though vascularity may be seen more prominently at 1 month follow-up, additional treatment should be carefully made in asymptomatic patients [13,22].

Even though EA is suggested as first line treatment for cystic or predominantly cystic nodules [14,28], repeated EA for recurrent cases has been reported as showing a markedly decreased treatment efficacy [6]. Thus, in the case of incompletely resolved initial clinical problems after EA, RFA has been introduced for additional treatment, rather than repeat EA [13,22]. Lee et al. [22] reported additional RFA for 27 patients who had incompletely resolved clinical problems after EA. All 27 patients showed therapeutic success. In a prospective study [13], RFA achieved 91% volume reduction in 22 of 94 patients who showed of incompletely resolved symptoms.
Although therapeutic success was achieved at 1-month follow-up, longer evaluation is necessary because of delayed recurrence. Suh et al. reported 24.1% (21/87) of delayed recurrence during an average follow-up of 10.1 months. Fourteen of 21 delayed recurrences treated with RFA showed 100% therapeutic success [2]. In our study, we experienced seven cases of delayed recurrence and underwent RFA for additional treatment, which showed therapeutic success with an average volume reduction ratio of 80.2%.

This study has several limitations. First, as this study is of a retrospective nature with patients from a single center, a selection bias may exist. Second, the included population is relatively small, which could reduce the sensitivity of the study results. Third, follow-up was undertaken using a telephone survey for 16 patients who did not make further follow-up visits after the first follow-up at 1 month after EA. We evaluated whether the patients had new symptoms or enlargement of nodules, and if they did not complain of any symptoms, their case was considered a therapeutic success. Thus, we could not evaluate a final US for these patients, and assumed the EA achieved its treatment goal as long as the 1-month follow-up US did not show any suspicious feature for recurrence and patients did not return to the clinic complaining of any symptom. Lastly, there is still potential for delayed recurrence in the future.

We suggest an additional management algorithm for thyroid nodules treated by EA, as depicted in Fig. 5. We recommend physicians who perform EA for cystic nodules to consider further alternatives such as observation or repeated pathologic confirmation in deciding treatment options based on patients’ clinical situation.
Conclusions

The decision on whether to perform additional treatment after EA for cystic or predominantly cystic thyroid nodules should be carefully decided using a combination of actual clinical problems and US features. Understanding of this concept will be useful for doctors who perform US-guided EA, assisting them in planning for additional procedures.
References


Figure Legends

Figure 1. Study population diagram.

Figure 2. A 64-year-old female patient.

At initial work-up, there was a predominantly cystic nodule with benign cytology on FNA in the left thyroid gland (a) with a volume of 28 ml. The initial cosmetic score and symptom score were both 4. The patient underwent ethanol ablation with 10 ml ethanol followed by 25 ml aspiration of cystic contents. At 1-month follow-up, the residual cystic volume was about 9 ml (b), but the symptoms had gone. The patient underwent regular follow-up rather than additional treatment, and the nodule had collapsed at the 24-month follow-up ultrasonography (c, volume: 0.5 ml; volume reduction ratio: 98.2%).

Figure 3. A 71-year-old female patient.

At initial work-up, there was a predominantly cystic mass of about 10.8 ml with benign cytology on FNA in the left thyroid lobe (a). The initial cosmetic score was 4, and the symptom score was 2. The patient underwent ethanol ablation with 5 ml ethanol followed by 10 ml aspiration of cystic contents. At 1-month follow-up, the residual cystic volume was 7.4 ml, which was <50% volume reduction (b). As she did not have any symptoms, the patient did not want to undergo additional treatment. She underwent regular follow-up without additional treatment, and the nodule had collapsed at the 36-month follow-up ultrasonography (c, volume: 0.7 ml; volume reduction ratio: 93.5%).

Figure 4. A 63-year-old female patient.

At initial work-up, there was a cystic mass of about 10 ml with benign cytology on FNA in the right thyroid lobe (a). The initial cosmetic score was 4, and the symptom score was 6. The patient underwent ethanol ablation with 5 ml ethanol followed by 10 ml aspiration of cystic contents. At 1-month follow-up, the size of the nodule had significantly decreased (2.6 ml, 75.2% volume reduction ratio) (b), but the nodule showed a solid component with vascularity that was not definitely seen in the initial examination. As her symptoms had dramatically reduced to a symptom score of 2 after ethanol ablation, the patient underwent observation without additional treatment. At the 32-month follow-up, immediate additional treatment was still not necessary, as there were no symptoms (volume: 1.3 ml; volume reduction ratio: 87.6%), even though there might be the possibility of recurrence in the long-term follow-up because of the solid component with vascularity (c).
Figure 5. Suggested additional treatment strategy after ethanol ablation.

*Symptom indicated on the figure includes cosmetic problems.

** Vascularity includes intranodular vascularity (grade 3 and 4).

FNA; fine needle aspiration

CNB; core needle biopsy
### Table 1. Efficacy of EA over the follow-up period

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before EA (n = 154)</th>
<th>1-month follow-up</th>
<th>(p)-value(^a)</th>
<th>Final follow-up</th>
<th>(p)-value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Largest diameter (cm)</td>
<td>3.9±1.4</td>
<td>2.3±4.2</td>
<td>&lt;0.0001</td>
<td>1.5±1.0</td>
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<tr>
<td>Nodule volume (ml)</td>
<td>18.4±21.6</td>
<td>4.2±6.5</td>
<td>&lt;0.0001</td>
<td>1.9±3.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vascularity</td>
<td>0.5±0.8</td>
<td>0.7±0.9</td>
<td>0.05</td>
<td>0.6±0.9</td>
<td>0.18</td>
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<tr>
<td>Volume reduction ratio</td>
<td></td>
<td>76.1±20.8</td>
<td></td>
<td>87.4±18.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Symptom score</td>
<td>2.6±2.0</td>
<td>0.7±0.9</td>
<td>&lt;0.0001</td>
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<td>Cosmetic score</td>
<td>3.9±0.6</td>
<td>2.3±0.9</td>
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\(^a\) A paired \(t\)-test was used to compare the variables between the initial assessment and 1-month follow-up.

\(^b\) A paired \(t\)-test was used to compare the variables between the 1-month and final follow-up.

Values reported as mean ± standard deviation
Table 2. Comparison of factors in the therapeutic success and failure groups for patients who would be considered for additional treatment according to the previously proposed criteria for recurrence at 1-month follow-up

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<th>Proposed criteria for additional treatment</th>
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<td>Residual fluid &gt;1 ml (n=32, 20.8%)</td>
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<td>6 (30.0%)</td>
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<td>Volume (ml)</td>
<td>7.6±7.2</td>
<td>18.8±16.2</td>
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<td>Solid component with vascularity (n=45, 29.2%)</td>
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Figure 2. A 64-year-old female patient. At initial work-up, there was a predominantly cystic nodule in the left thyroid gland (a) with a volume of 28 ml. The initial cosmetic score and symptom score were both 4. The patient underwent EA with 10 ml ethanol followed by 25 ml aspiration of cystic contents. At 1 month follow-up, the residual cystic volume was about 9 ml (b), but the symptoms had gone. The patient underwent regular follow-up rather than additional treatment, and the nodule had collapsed at the 24 month follow-up ultrasonography (c, volume: 0.5 ml; volume reduction ratio: 98.2%).
Figure 3. A 71-year-old female patient. At initial work-up, there was a predominantly cystic mass of about 10.8 ml in the left thyroid lobe (a). The initial cosmetic score was 4, and the symptom score was 2. The patient underwent EA with 5 ml ethanol followed by 10 ml aspiration of cystic contents. At 1 month follow-up, the residual cystic volume was 7.4 ml, which was <50% volume reduction (b). As she did not have any symptoms, the patient did not want to undergo additional treatment. She underwent regular follow-up without additional treatment, and the nodule had collapsed at the 36 month follow-up ultrasonography (c, volume: 0.7 ml; volume reduction ratio: 93.5%).
Figure 4. A 63-year-female patient. At initial work-up, there was a cystic mass of about 10 ml in the right thyroid lobe (a). The initial cosmetic score was 4, and the symptom score was 6. The patient underwent EA with 5 ml ethanol followed by 10 ml aspiration of cystic contents. At 1 month follow-up, the size of the nodule had significantly decreased (2.6 ml, 75.2% volume reduction ratio) (b), but the nodule showed a solid component with vascularity that was not definitely seen in the initial examination. As her symptoms had dramatically reduced to a symptom score of 2 after EA, the patient underwent observation without additional treatment. At the 32 month follow-up, immediate additional treatment was still not necessary, as there were no symptoms (volume: 1.3 ml; volume reduction ratio: 87.6%), even though there might be the possibility of recurrence in the long-term follow-up because of the solid component with vascularity (c).
Figure 5. Suggested additional treatment strategy after ethanol ablation. *Symptom indicated on the figure includes cosmetic problems. ** Vascularity includes intranodular vascularity (grade 3 and 4). FNA; fine needle aspiration CNB; core needle biopsy.