Ultrasonography-guided ethanol ablation of predominantly solid thyroid nodules: a preliminary study for factors that predict the outcome

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Objectives: The aim of this study was to evaluate the success rate in ultrasonography-guided ethanol ablation (EA) of benign, predominantly solid thyroid nodules and to assess the value of colour Doppler ultrasonography in prediction of its success.

Methods: From January 2008 to June 2009, 30 predominantly solid thyroid nodules in 27 patients were enrolled. Differences in the success rate of EA were assessed according to nodule vascularity, nodule size, ratio of cystic component, amount of injected ethanol, degree of intranodular echo-staining just after ethanol injection and the number of EA sessions.

Results: On follow-up ultrasonography after EA for treatment of thyroid nodules, 16 nodules showed an excellent response (90% or greater decrease in volume) and 2 nodules showed a good response (50–90% decrease in volume) on follow-up ultrasonography. However, 5 nodules showed an incomplete response (10–50% decrease in volume) and 7 nodules showed a poor response (10% or less decrease in volume). Statistical analysis revealed a significant association of nodule vascularity ($p=0.002$) and degree of intranodular echo-staining just after ethanol injection ($p=0.003$) with a successful outcome; however, no such association was observed with regard to nodule size, ratio of cystic component, amount of infused ethanol and the number of EA sessions. No serious complications were observed during or after EA.

Conclusion: The success rate of EA was 60%, and nodule vascularity and intranodular echo-staining on colour Doppler ultrasonography were useful in predicting the success rate of EA for benign, predominantly solid thyroid nodules.

Received 14 December 2010

Revised 8 May 2011

Accepted 17 May 2011

DOI: 10.1259/bjr/81849588

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Livraghi et al [1] used ultrasonography-guided ethanol ablation (EA) for the treatment of hyperfunctioning thyroid nodules; EA has since been established as the first-line treatment for benign cystic thyroid nodules, and may be considered an appropriate alternative to clinical follow-up, radioiodine therapy or thyroid surgery for treatment of autonomous functioning thyroid nodules (AFTNs) or toxic nodules. Advantages of EA include low risk, low cost, practicability in the outpatient clinic and ease of performance [2–14]. However, radioiodine therapy and surgery remain the treatments of choice for large toxic thyroid nodules [5, 8, 9, 15].

Following the initial use of EA in the treatment of benign cystic thyroid nodules [16], many published studies have reported appreciable efficacy of EA in the treatment of benign cystic thyroid nodules and recurrent cystic nodules [17–26]. However, published data regarding the EA of solid thyroid nodules have shown varying

results, depending on nodule size, the volume of ethanol instilled and the presence of nodule toxicity (Table 1) [2–14]. Thus, the use of EA in the treatment of solid thyroid nodules has been limited owing to controversy over its efficacy and clinical indications. Several studies have attempted to determine factors that might be predictive of the effectiveness of EA in AFTNs or toxic nodules. These studies found that an initial nodule volume [5, 8–10] and the presence of a cystic component making up more than 30% of the total volume are important factors in predicting a positive response to EA [14]. Despite these results, EA is rarely selected for the treatment of a solid thyroid nodule compared with the options of clinical follow-up, radioiodine therapy or surgery. Identification of factors that might aid in the accurate prediction of the success of EA in the treatment of solid thyroid nodules could result in more frequent clinical use of EA. To the best of our knowledge, no study of the feasibility of colour Doppler ultrasonography for predicting the success in EA of predominantly solid thyroid nodules has been conducted to date.

The aim of this study was to perform an evaluation of the success rate in EA of benign, predominantly solid thyroid nodules and to assess the value of colour Doppler ultrasonography in predicting its success.

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This work was supported by the Busan Paik Hospital Imaging Research Institute.

Table 1. The published data of ethanol ablation for solid thyroid nodules

Reference number in present study	First author	Year	Type of nodules	Number of patients	Number of sessions	Success rate (%)	Major complication
2	Martino	1992	AFTN	37	1–3	100 ^a	No
3	Mazzeo	1993	AFTN	32	3–10	100 ^a	No
4	Papini	1993	Toxic	20	3–8	100 ^a	No
5	Livraghi	1994	AFTN	101	4–8	58.4 ^b	No
6	Goletti	1994	Cold	20	1–3	100 ^a	No
7	Bennedbak	1995	Cold	13	1	43 ^a	No
8	Di Lelio	1995	AFTN	31	3–7	77 ^b	No
9	Lippi	1996	AFTN	429	2–12	74.6 ^a	No
10	Monzani	1997	Toxic	117	5–10	77.9 ^b	No
11	Zingrillo	1998	Cold	41	2–8	92.7 ^a	No
12	Tarantino	2000	AFTN	12	4–11	100 ^a	No
13	Kim	2003	Solid	22	1–3	35 ^a	No
14	Guglielmi	2004	AFTN	112	2–7	64.2 ^a	No

AFTN, autonomous functioning thyroid nodule.

^aA success means 50% or more volume reduction rate.

^bComplete cure of toxic nodule means that both free thyroid hormone and thyrotropin serum levels returned within the normal range.

Methods and materials

Patients

Our institutional review board approved this study. From January 2008 to June 2009, 27 patients who complained of a palpable anterior neck mass and who chose to undergo EA after recommendation of EA for treatment were included. We simultaneously treated two nodules in each of the three patients. A single radiologist performed EA of 30 benign, predominantly solid thyroid nodules (defined as a nodule with a cystic component comprising less than 50% of the total volume) in 27 patients (19 females, 8 males; age range 16–62 years; mean age 38.0 years). None of the thyroid nodules showed malignant ultrasonography findings before EA, and each was confirmed as benign after one or two sessions of ultrasonography-guided fine-needle aspiration biopsy. To avoid the possibility of inadvertently treating a follicular carcinoma, follicular neoplasm after aspiration cytology was also excluded. None of these patients had a history of diffuse thyroid disease and all fell within normal range for serum thyroid hormone, thyrotropin and thyroid peroxidase antibody levels before EA, except for three patients with a low thyrotropin serum level. Serum thyroid hormone (total triiodothyronine; normal range 80–200 ng dL⁻¹), free thyroxine (normal range 0.93–1.71 ng dL⁻¹), thyrotropin (normal range 0.27–4.20 mIU L⁻¹) and thyroid peroxidase antibody (normal range 0–35 IU mL⁻¹) levels were determined by chemiluminescent immunoassay (Modular E170; Roche, Mannheim, Germany). Routine scintiscans were not included in this study. Nodule volume was calculated by means of the ellipsoid formula (width × length × height × 0.52).

Colour Doppler ultrasonography

Each nodule was evaluated with real-time thyroid ultrasonography, including a colour Doppler study before EA. Thyroid ultrasonography was performed by a single radiologist (DWK) using a high-resolution

ultrasound instrument (iU22; Philips Medical Systems, Bothell, WA) equipped with a 12–5 MHz linear probe. During the colour Doppler ultrasonography examination, a low value of pulse repetition frequency, 700 Hz, was used for evaluation of the vascularity of thyroid nodules. Nodule vascularity was compared with adjacent normal parenchymal vascularity on real-time colour Doppler ultrasonography and classified as follows: scanty vascularity (no vascular signal or only a few vascular spots), low vascularity (the vascular signal is lower than that of adjacent normal parenchyma), isovascularity (the vascular signal is the same as that of adjacent normal parenchyma), mildly increased vascularity (the vascular signal is greater than that of adjacent normal parenchyma and covers ≤30% of the solid portion) and markedly increased vascularity (the vascular signal covers at least 30% of the solid portion). Categories were determined on the basis of real-time colour Doppler ultrasonography performed by the radiologist just prior to the EA procedure. Discrete ultrasonography features usually associated with diffuse thyroid disease were not observed in any of the patients.

Technique of ethanol ablation

Written informed consent was obtained from all patients prior to each EA. EA was performed on an out-patient basis by a radiologist according to the following method. The operator used an empty 10-ml plastic syringe attached to either a conventional 21- or 23-gauge needle (23 gauge for a purely solid nodule or a predominantly solid nodule with a smaller cystic component, and 21 gauge for a predominantly solid nodule with a larger cystic component). During the entire procedure, the operator manoeuvred the ultrasonography probe with his left hand and the syringe–needle unit with his right hand. The ultrasonography probe was adjusted for centring the target nodule on the ultrasonography monitor. The needle was inserted rapidly almost perpendicular to the neck while the operator applied positive pressure to the syringe piston using the thumb of his right hand in order to prevent an influx of blood into the needle

lumen. The method of ethanol instillation differed according to whether the nodule was purely solid or predominantly solid. In the case of a purely solid nodule, absolute ethanol (99.9%) injection was administered directly. Adequate coverage of the target nodule, as indicated by its echogenicity (called intranodular echo-staining), was achieved by adjusting the injection of ethanol under ultrasonography guidance; the needle-syringe unit was then rapidly withdrawn and the procedure was completed. In cases where the predominantly solid nodule contained a cystic component, the cystic component was punctured and almost completely aspirated, and an appropriate amount of ethanol was instilled. After replacement of the needle into the solid component of the target nodule by adjustment of the needle position, an appropriate amount of ethanol, which was in proportion to nodule size and echo-staining of the solid portion of the nodule, was infused. A single-puncture technique was used with no local anaesthesia. In all cases the amount of injected ethanol did not exceed 10 ml. Any patient experiencing a sensation of drunkenness after EA was not allowed to drive herself/himself home. Additional EA was performed 1–2 months after the initial EA when the outcome of EA was determined to be unsuccessful on follow-up ultrasonography. The amount of infused ethanol, degree of intranodular echo-staining just after ethanol injection and presence of pain or other complications during or after the procedure were recorded for each patient.

Ultrasonography follow-up

Nodule volume was calculated during the latest thyroid ultrasonography before EA and during the final follow-up thyroid ultrasonography after EA. The difference in nodule volume was used as a criterion for determination of the success or failure of EA for treatment of thyroid nodules. The other factor was the absence of, or marked reduction in, nodule vascularity. The outcome of EA was classified as follows, according to the decrease in nodule volume and nodule vascularity: poor response ($\leq 10\%$ decrease in volume, regardless of nodule vascularity), incomplete response (10–50% decrease in volume, regardless of nodule vascularity), good response (50–90% decrease in volume and decreased vascularity) and excellent response ($\geq 90\%$ decrease in volume and scanty vascularity). On real-time colour Doppler ultrasonography, nodule vascularity on the same-day ultrasonography, just before ethanol injection, and that of the last follow-up ultrasonography after EA were compared. Also, nodule volume measured on the same-day ultrasonography just before ethanol injection and that of the last follow-up ultrasonography after EA were compared. Furthermore, the success rate of EA was compared across the nodule size, ratio of the cystic component, amount of infused ethanol, degree of intranodular echo-staining by injected ethanol and the number of sessions of EA. Intranodular echo-staining was roughly estimated on the basis of real-time ultrasonography just after EA and classified as follows: no staining (nearly complete washout of injected ethanol), poor staining ($\leq 10\%$ of the injected area), mild staining (10–50% of the injected area) and moderate staining ($\geq 50\%$ of the injected area) (Figure 1).

Statistical analysis

Using the Kruskal–Wallis test or Fisher's exact test, the success rate of EA was compared across nodule vascularity, nodule size, ratio of cystic component, amount of infused ethanol, degree of intranodular echo-staining and the number of sessions of EA. SPSS software (SPSS, Inc., Chicago, IL) was used for all statistical evaluation. A two-tailed p -value < 0.05 was considered statistically significant.

Results

EA of 30 benign, predominantly solid thyroid nodules (mean of the largest diameter, 2.9 cm; range of the largest diameter, 1.5–5.7 cm) was performed in 27 patients. All patients had normal thyroid hormone serum levels during the follow-up period (3–6 months after the final session). Of three patients who had a low serum thyrotropin level before EA, one patient still showed a low normal serum thyrotropin level after EA. The other 26 patients had a normal serum thyrotropin level during the follow-up period.

Results of EA for 30 solid thyroid nodules are listed in Table 2. Successful treatment was achieved in 18 nodules (60%). Of these, one showed scanty vascularity, eight showed low vascularity, seven showed iso-vascularity and two showed mildly increased vascularity, as determined by colour Doppler ultrasonography (Figure 2). For the nodules showing a successful response, follow-up ultrasonography was performed over a 12-month period (mean 18.5 months; range 12–30 months). Five nodules, which comprised four with isovascularity and one with mildly increased vascularity, were regarded as showing an incomplete response (10–50% decrease in volume); however, the patients felt a slight improvement in their symptoms (such as palpable lumps). For the nodules showing an incomplete response, follow-up thyroid ultrasonography was performed over a 6-month period (mean 13.8 months; range 6–22 months), and radiofrequency ablation (RFA) was performed for two nodules showing an incomplete response. Seven nodules, which included four with mildly increased vascularity and three with markedly increased vascularity, were regarded as having a poor response ($\leq 10\%$ decrease in volume). For all nodules showing a poor response, RFA was performed without long-term ultrasonography follow-up.

Nodules with low vascularity showed a high success rate for EA despite undergoing only one or two sessions, as compared with nodules with high vascularity ($p=0.002$). Nodules showing high staining by injected ethanol yielded significantly better results than those with poor staining ($p=0.003$). Based on statistical analysis, nodule vascularity and degree of intranodular echo-staining just after ethanol injection showed significant correlation with the success rate; however, nodule size ($p=0.077$), the ratio of cystic component to thyroid nodule ($p=0.641$), the amount of infused ethanol ($p=0.264$) and the number of EA sessions ($p=1.0$) showed no significant relationship with success rate.

13 patients experienced mild pain either during or several minutes after the procedure (13/27, 48.1%).

Figure 1. Four classifications of intranodular echo-staining in greyscale ultrasonography. According to the degree of intranodular echo-staining (arrows) during and just after ethanol injection, a thyroid nodule was classified as (a) no staining, (b) poor staining, (c) mild staining and (d) moderate staining.

However, only one patient took oral analgesic for 1 day for management of local pain. No serious complications occurred during or after EA.

Discussion

Owing to its ease of use, safety, low cost and effectiveness, EA is the first-choice tool for use in the treatment of benign cystic thyroid nodules [17–26]. However, the efficacy and results of EA for the treatment of solid or predominantly solid thyroid nodules have been variable according to studies (Table 1) [2–14]. RFA or laser ablation has recently become a safe modality for use as an appropriate alternative to clinical follow-up, radioiodine therapy, surgery and EA treatment of benign solid thyroid nodules [27–30]. RFA has proven to be a feasible and effective tool for treatment of solid nodules; however, its disadvantage lies in the high cost when compared with EA. Baek et al [29] suggested that RFA for the treatment of benign, predominantly solid thyroid nodules is effective for the reduction of nodule volume and relief of nodule-related clinical problems; they demonstrated a high success rate (100%) and a high mean volume reduction rate (79.7%) during a 6-month period of ultrasonography follow-up. In the present study, the mean success rate

(60%) and volume reduction rate (64.3%) of EA were lower than those reported by Baek et al [29].

In this study, a significant relationship was observed between nodule vascularity and the success rate of EA. EA of predominantly solid thyroid nodules with high vascularity on colour Doppler ultrasonography showed worse results than those with low vascularity. In addition, venous washout of injected ethanol was frequently observed during EA of solid thyroid nodules with high vascularity. We found that poor venous washout of injected ethanol during EA was closely related to good intranodular echo-staining and good results, whereas moderate venous washout was closely related to poor intranodular echo-staining and poor results. Consequently, intranodular echo-staining is closely related to the success rate of EA. It may be hypothesised that effective ethanol ablation is possible only when the ethanol stays within the thyroid nodule and there is no venous washout of the injected ethanol. A long stay of ethanol with little washout can have an effect on sclerotic mechanisms of ethanol, which include coagulative necrosis, small-vessel thrombosis and haemorrhagic infarction [31]. Therefore, EA may become the first-line treatment when a symptomatic solid thyroid nodule shows low- or isovascularity in colour Doppler ultrasonography.

Table 2. Results of ethanol ablation for 30 predominantly solid thyroid nodules

Sex/age (years)	Size (cm)	Volume (ml)	CP (%)	NVas	AmIE (ml)	IES	NoS	VRR (%)	Result	LFUUS (months)
F/60	3.5	11.1	30	1	2	3	1	91.8	Excellent	26
F/45	2.2	3.3	50	2	2.5	3	1	92.3	Excellent	30
M/49	1.8	1	0	2	1.3	1	1	41.2	Incomplete	13
M/27	2.5	3.5	0	3	2	0	1	0	Poor	6
F/29	2	1.3	35	1	1	3	1	99	Excellent	28
F/50	1.9	2.4	0	4	2	0	1	0	Poor	6
M/54	1.8	1.9	25	2	1	3	1	98.3	Excellent	16
F/22	3.5	7.5	35	2	2.5	1	1	48.6	Incomplete	22
F/22	1.9	1.4	0	2	1	1	1	47.1	Incomplete	22
F/34	1.5	1.3	0	2	1	2	1	79.8	Good	20
F/28	3.9	13.8	5	3	3	0	1	5.7	Poor	6
F/18	3.7	12.1	35	2	5	2	2	98.6	Excellent	17
F/18	2.2	2	0	1	1	3	1	99.4	Excellent	17
F/28	1.7	1.1	50	3	3	3	1	79.7	Good	21
F/32	2.5	3	5	2	2	1	2	97.4	Excellent	18
F/31	1.6	1.6	45	1	1	3	1	98.5	Excellent	15
F/54	3.7	15.4	50	1	5	2	1	96.5	Excellent	16
F/29	3.7	16.2	30	1	1	3	1	96.8	Excellent	21
F/16	2.7	4.4	40	2	1.5	3	1	98.1	Excellent	17
M/49	3	9.2	20	3	3	1	2	95.6	Excellent	14
M/48	4.8	16.5	5	4	4	1	1	0	Poor	6
F/28	4.4	20.5	10	4	3	2	1	0	Poor	6
F/25	2.3	1.9	0	3	1.5	3	1	0	Poor	6
M/57	2	2.5	20	0	1	3	1	98.7	Excellent	13
F/42	2.3	2.3	50	1	1	3	1	99.9	Excellent	13
M/43	3.5	14.2	40	2	4	2	1	38.3	Incomplete	14
M/25	3.8	17.3	20	3	4.5	2	2	5.4	Poor	6
M/25	2.5	3	10	2	1	2	1	96.4	Excellent	12
F/28	2.9	6.7	40	1	2	2	1	96.7	Excellent	16
F/62	5.7	52.2	50	3	5.5	2	2	29.7	Incomplete	6
Mean	2.9	8.4	23.3		2.3		1.2	64.3		15.0

AmIE, the amount of injected ethanol in the first EA session; CP, cystic percentage before EA; EA, ethanol ablation; F, female; LFUUS, last follow-up ultrasonography; M, male; NoS, number of EA sessions; VRR, volume reduction rate.

Size column indicates the largest diameter of the nodule.

NVas indicates nodule vascularity before EA: 0, no vascularity; 1, low vascularity; 2, iso-vascularity; 3, mildly increased vascularity; 4, markedly increased vascularity.

IES indicates intranodular echo-staining, depending on the degree of nodule echogenicity due to infused ethanol: 0, no staining (nearly complete washout); 1, poor staining ($\leq 10\%$); 2, mild staining ($10\text{--}50\%$); 3, moderate staining ($\geq 50\%$).

Result, depending on decrease in nodule volume: poor, $\leq 10\%$; incomplete, $10\text{--}50\%$; good, $50\text{--}90\%$; excellent, $\geq 90\%$.

Only one or two EA sessions were conducted for each nodule in this study. We restricted additional EA sessions in case of a significant appearance of venous washout of the injected ethanol during the procedure or poor intranodular echo-staining immediately after ethanol injection; therefore, no more than two EA sessions were conducted. Furthermore, depending on nodule vascularity, degree of intranodular echo-staining and an unsuccessful result on follow-up ultrasonography, an additional EA session or RFA can be decided upon; thus, three or more EA sessions can be avoided.

The fact that EA of large solid thyroid nodules is less successful than EA of small ones is generally accepted [5, 8, 9, 14, 24]; however, other studies have demonstrated safe and effective techniques for treatment of large (>30 ml) hyperfunctioning nodules [12]. Some investigators have emphasised that a higher dose of ethanol per session is more important than nodule size and could be significantly related to EA success [12]. However, we believe that intranodular echo-staining of the injected

ethanol with no washout is more important than nodule size or the amount of ethanol injected per session.

Kim et al [13] insisted that the volume of instilled ethanol showed significant correlation with the volume reduction rate of cysts, but not that of solid nodules. The percentage of cystic components in the thyroid nodule has been shown to be closely associated with successful EA [14]. However, in the present study, nodules with a higher percentage of cystic components did not show good results in comparison with nodules with a lower percentage of cystic components. If the procedure were applied to predominantly solid thyroid nodules with low vascularity and high echo-staining without venous washout, we could expect a higher success rate before and during EA. Using this guideline for the selection of thyroid nodules, we could improve the therapeutic results of benign predominant thyroid nodules by choosing the most efficient therapeutic modality.

Ablation mechanisms of ethanol include coagulative necrosis and small-vessel thrombosis with haemorrhagic

Figure 2. A case of successful ultrasonography-guided percutaneous ethanol ablation (EA). Longitudinal (a) greyscale and (b) colour Doppler ultrasonography images of a thyroid nodule in the right lobe in a 32-year-old female showing low vascularity (about $1.3 \times 1.8 \times 2.5$ cm). Follow-up ultrasonography images at (c) 5 and (d) 18 months after the second session of EA show moderate shrinkage (about $0.8 \times 0.9 \times 1.3$ cm; about 84% decrease in volume) and marked shrinkage (about $0.5 \times 0.5 \times 0.6$ cm; about 97.4% decrease in volume), respectively.

infarction [31]. An ablated portion of the nodule is replaced by a granulation tissue, followed by progressive shrinkage. Except for transient neck pain and discomfort, there was no occurrence of serious complications of EA in our study. We think that the most serious complication is necrosis of the adjacent normal soft and nerve tissue by leakage of injected ethanol [11, 15, 32]. To avoid complications, substantial experience and a precise ultrasound-guided injection are required. For reduction of side effects, the amount of ethanol injected during each session did not exceed 10 ml in our study. There is no definite guideline for an adequate amount of ethanol injected; in other studies, the maximum amount of ethanol injected per session varied from 7 to 14 ml without serious complication [9, 11, 12].

There were several limitations to our study. First, the sample size was small and the range of nodule sizes or configurations broad. Therefore, large-scale studies are recommended in the future. Second, objective quantification of nodule vascularity, intranodular echo-staining and venous washout of injected ethanol was not performed. These were estimated and subsequently classified by the ultrasonography operator. Finally, a thyroid scan was not performed before EA.

In summary, the success rate of EA was 60%, and EA of predominantly solid nodules was more effective in less vascular and more echo-staining thyroid nodules than in more vascular and less echo-staining ones. Therefore, colour Doppler ultrasonography may be a useful tool for the prediction of treatment outcomes for EA of benign, predominantly solid thyroid nodules.

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