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Ultrasound-Guided Percutaneous Ethanol Ablation for the Management of Recurrent Thyroid Cancer: Evaluation of Efficacy and Impact on Disease Course

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Background and Objectives: Neck recurrences of thyroid cancer are frequently detected in routine ultrasound (US) follow-up. Broad management of these lesions may include active surveillance, surgery or local percutaneous techniques, but for the latter, little is known about impact on long-term follow-up and need of subsequent radioactive iodine (RAI) therapy. **Materials and Methods:** 42 patients underwent US-guided ethanol ablation (EA) over 71 thyroid bed or lymph node confirmed recurrences. All volume reduction >50%, absence of power Doppler signal and fine needle aspiration (FNA) washout thyroglobulin (Tg) value <1 ng/mL should be present to consider a complete ablation. Patients with TNM stage I-II, ≤2 lesions and/or baseline plasma TSH-suppressed Tg level <0.2 ng/mL did not undergo post-EA RAI therapy. Post-EA plasma Tg values were compared to baseline in patients with and without subsequent RAI therapy. **Results:** 62 lesions (87.32%) achieved a complete ablation after a mean follow-up of 40.5 months (range, 12-73). Four treated lesions (5.63%) recurred (3/39 and 1/32 in patients with and without subsequent RAI therapy), and 7 patients (16.66%) developed new recurrences throughout follow-up (5/19 and 2/23 with and without RAI therapy). Both plasma TSH-suppressed and TSH-stimulated Tg levels descended after EA in both groups, and 17/38 (44.73%) patients achieved a TSH-suppressed Tg <0.2 ng/mL, with no differences between both groups of patients. All EA procedures were conducted safely without serious or persistent side effects. **Conclusion:** Successful EA were achieved safely in 87.32% of patients with recurrent thyroid cancer, with a positive effect on systemic disease as reflected by plasma post-EA Tg levels. A subset of patients with TNM stage III, ≤2 lesions and/or low pre-EA plasma Tg levels may not need subsequent RAI therapy after successful ablation. Overall, EA is an effective and balanced therapy for selected patients with neck recurrent thyroid cancer as an alternative to surgery.

Key Words: Ultrasound guided ethanol ablation, Recurrent thyroid cancer, Low risk papillary cancer

Introduction

Differentiated thyroid cancer (DTC) is one of the most common types of endocrine malignancy, accounting for more than 80% of all thyroid cancers,[1,2] with an increasing prevalence worldwide.[3,4] Usually, DTC presents with an excellent prognosis, specially the most frequent histological type papillary thyroid cancer (PTC). Indeed, survival rates for PTC in patients

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without distant metastatic disease are similar to that of general population.[5-7] In this favourable context, it becomes mandatory to individualize available treatment strategies on the basis of risk stratification, in order to minimize treatment-derived comorbidities and reduce the economic and psychological burden that these treatments may represent for sanitary systems and for the patients themselves, respectively.[8,9]

Despite its excellent prognosis, DTC presents a recurrence rate in the neck that ranges from 20% to 59%, according to low or high risk of recurrence categories, respectively.[9-11] Rescue surgery including lymphadenectomy of involved anatomical compartments of the neck, followed by radioactive iodine (RAI) ablation therapy remains as the standard of care for these patients.[6,8] Nevertheless, the risk of complications associated to rescue surgery is high due to the distortion of the neck anatomy as a result of scar tissue formation, particularly in patients with repeated neck dissections[12,13] and those involving the central compartment.[14] Even more, with this strategy only 30 to 50% of patients will arrive to complete biochemical remission.[15-17]

The progressively increasing use of routine high-resolution neck ultrasound (US) in the follow-up of patients with thyroid cancer is resulting in a growing incidence of patients with fine needle aspiration (FNA) cytology-confirmed small size (from 2-3 to 5 mm) lymph node regional disease.[18] A correct approach to the management of this situation represents a clinical dilemma, as to date, a proactive management of this low tumoral burden with surgery has not proven to result in an improvement of patient's overall survival, and conversely, an increase in the risk of complications is associated to classical therapeutic interventions.[19] In this setting, US-guided ablation techniques, including ethanol ablation (EA) have been reported to represent highly effective therapeutic options with a low risk of complications, well balanced between active surveillance and surgical reintervention. Authors have reported high rates of successful ablation following ethanol percutaneous injection for recurrent thyroid cancer, even after long-term follow-up.[20-27] Nevertheless, most reported series include small numbers of patients without control groups and lack of standardisation on US and biochemical criteria used to define a successful ablation procedure. Furthermore, little information is available on long-term impact of EA on the course of the disease. Finally, in this emerging context, no specific guidelines have been issued for EA procedures so far.

In this paper, we present the results of US-guided percutaneous EA in a series of outpatients with thyroid cancer local and/or regional lymph node recurrence, who underwent serial EA procedures performed in the setting of a high-resolution US thyroid consult. Primary objectives of this prospective study included evaluation of predefined biochemical and US-based imaging criteria for considering a complete ablation procedure and evaluation of safety, proposing standardized criteria for the evaluation of EA results. Secondary objective included evaluation of the impact of EA on the clinical course of the disease based upon changes in plasma thyroglobulin (Tg) measurements in patients without known distant metastatic disease. Additionally, patients were initially classified according to further risk of new recurrence in order to receive or not subsequent RAI therapy, aiming to determine whether a subgroup of low-risk patients undergoing EA might benefit from just active surveillance rather than subsequent RAI therapy.

Materials and Methods

From June 2013 to May 2019, a total of 42 patients with a diagnosis of thyroid cancer who underwent US-guided percutaneous EA on a total of 71 lesions identified either as thyroid bed recurrence or lymph node metastases, were consecutively included in this study. All US detected lesions were confirmed by FNA cytology and/or measurement of Tg in FNA washouts. Decision on EA procedure versus active surveillance or surgical reintervention was taken in a multidisciplinary committee, including endocrinologists, surgeons and specialists in Nuclear Medicine, according to best clinical judgement and accepted international guidelines including: high-risk or contraindication for surgery, a number equal or less than 3 lesions per anatomical

neck compartment of less than 1 cm that are accessible to US-guided needle puncture or refusal of surgery by patients.[28,29] None of the patients included had evidence of distant metastatic disease. All patients gave written informed consent as part of routine requisites before undergoing EA procedures. Because EA is part of our routine medical management for neck recurrences of DTC, this study did not require approval by our institution's Ethics Committee.

Patients

Baseline characteristics of patients are shown in Table 1. Most patients harboured a low risk postoperative TNM stage I or II thyroid cancer, according to the American Joint Committee on Cancer staging system.[30] Forty patients presented histological variants of PTC and two more patients presented a follicular thyroid cancer (FTC) and an oncocytic variant of FTC, respectively. All patients had undergone initial total thyroidectomy with (17 patients) or without (25 patients) lateral lymph node resection, followed by initial ablative RAI therapy. Up to 13 patients had undergone previous rescue surgery (lateral neck dissection and/or thyroid bed reintervention) followed by RAI therapy. As per our protocol, patients without known lymph node neck disease after initial surgery received an initial ablative dose of 100 millicurie (mCi) of radioiodine, whereas patients with lymph node involvement received 150 mCi. All patients undergoing rescue surgery did undergo additional ablation RAI therapy with 150–200 mCi. Twenty three patients with a postoperative TNM stage I or II, or a baseline thyroid stimulating hormone (TSH) suppressed plasma Tg <0.2 ng/mL or ≤ 2 confirmed lesions, were considered a

Table 1. Baseline characteristics of patients

	Total	No post-EA RAI treatment group	Post-EA RAI treatment group
Patients (n)	42	23	19
Sex (n/% female)	25/59.52%	15/62.5%	10/55.55%
Age, years (mean±SD)	48.34±18.03	46.05±17.46	51.13±19.62*
Time from surgery to EA, years (mean/range)	3.72/0.5-18.0	3.83/0.5-18.0	3.54/0.5-6.3
Lateral neck dissection (n)	17	5	12
Rescue surgery+RAI (n)	13	3	10
RAI dose, mCi (mean±SD)	160.23±88.28	118.69±52.07	210.52±98.00*
Patients with Tg-Ig	4	1	3
TNM postoperative stage (n)			
I	23	16	7
II	8	5	3
III	5	1	4
IVA	6	1	5
IVB	0	0	0
Histology			
Classic PTC	23	14	9
PTCFV	5	3	2
PDPTC	1	0	1
MPTC	1	1	0
MFPTC	7	5	2
PTC with aggressive histology[§]	3	0	3
FTC	1	0	1
Oncocytic variant FTC	1	0	1

EA: ethanol ablation, FTC: follicular thyroid carcinoma, mCi: millicurie, MFPTC: multifocal papillary thyroid carcinoma, MPTC: micropapillary thyroid carcinoma, PDPTC: poorly differentiated papillary thyroid carcinoma, PTC: papillary thyroid carcinoma, PTCFV: papillary thyroid carcinoma follicular variant, RAI: radioactive iodine, SD: standard deviation, Tg-Ig: thyroglobulin antibodies

[§]Aggressive histology included one case with tall cell variant PTC and two cases with diffuse sclerosing variant PTC. *$p<0.05$ (two-sided t-Student)

low risk group and initially were not scheduled to undergo subsequent RAI therapy upon completion of EA (namely, No RAI treatment group), as opposed to 19 patients with TNM stage III or IV, or baseline TSH-suppressed plasma Tg >2 ng/mL or >2 confirmed lesions involving ≥2 neck anatomical compartments who completed ablative RAI therapy after EA (RAI treatment group). Two patients with postoperative stages III and IVa, respectively, were included in the No RAI treatment group, based upon a single lesion detected on US and baseline TSH-suppressed plasma Tg <0.2 ng/mL. Additionally, up to five patients with advanced postoperative TNM stage and/or aggressive histology were included for EA. This decision was based upon a low tumoral burden and low plasma Tg levels in most cases. One 72-year-old woman rejected surgery for a follicular carcinoma thyroid bed recurrence and EA was offered as alternative therapy. On average, EA procedures were performed 3.66 (mean) years after initial surgery (range, 0.5-18 years).

Table 2 shows baseline characteristics of lesions. A total of 71 lesions underwent percutaneous EA. Most treated lesions were lymph nodes (77.63%) as compared to 22.36% recurrent tumors in the thyroid bed, and most lymph nodes were located both in the lateral compartment around the carotid sheath and in the central compartment, which is in line with usual presentation of neck recurrences in thyroid tumors. A patient with an oncocytic variant of FTC developed FNA-cytology confirmed metastatic lesions located in the left sternocleidomastoids (ECM) muscle (two round well-defined nodules on US) and subcutaneous tissue (two round nodules under the skin scar) 3 years after initial thyroidectomy.

Methods

1) Neck US, FNA Cytology and Thyroglobulin Measurement

Routine neck US studies were performed with a Logic Q-6 device (General Electrics, Boston, MA, USA) equipped with a linear 9-13 MHz probe and with power Doppler signal, operated by two experienced endocrinologists. US-guided FNA cytology, when clinically indicated, was performed with 25G 2 cm or 21G 4 cm needles, and samples were prepared for liquid cytology with Citolyt solution (Hologic UK LTD, West Sussex, UK). Tg determination in needle washouts was performed according to a previously described technique.[31] A threshold of 1 ng/mL was considered positive for thyroglobulin-producing tissue. Plasma and FNA washout Tg levels were measured using an immunometric chemiluminescent assay (Cobas e411, Roche Diagnostics, Manheim, Germany) calibrated to

Table 2. Baseline characteristics of lesions

	Total	No post-EA RAI treatment	Post-EA RAI treatment
Patients (n)	42	23	19
Lesions (n)	71	32	39
n per patient	1.69±1.09	1.39±0.87	2.05±1.26*
Volume (mm^3), mean±SD	421±746	409±714	439±768*
Thyroid bed (n/%) persistence/recurrence	16 (22.36%)	6 (18.75%)	10 (25.64%)
Lymph node (n/%) metastases	55 (77.63%)	26 (81.25%)	29 (74.35%)
Neck region			
II	5	2	3
III-IV	42	23	19
VA-VB	8	3	5
VI	12	4	8
Skip metastasis[§]	4	0	4

EA: ethanol ablation, RAI: radioactive iodine, SD: standard deviation
[§]A patient with oncocytic variant follicular thyroid carcinoma presented with 4 seed metastases located at left sternocleidomastoids muscle (2) and subcutaneous fat tissue (2).
*$p<0.05$ (two-sided t-Student)

the CRM 457 standard with a functional sensitivity of 0.1 ng/mL and an intra-assay coefficient of variation (CV) of 5.05 and 4.49% at a mean dose level of 0.98 and 24.6 ng/mL, respectively (the minimum detectable Tg was 0.2 ng/mL until 2015 and subsequently 0.04 ng/mL). Measurement of anti-Tg antibodies (TgAb) was carried out using a chemiluminescent sequential immunometric assay (Architect I-2000 SR, Abbott Diagnostics, Middletown, VA, USA), calibrated to the World Health Organization 1st International Reference Preparation 65/93 standard, in order to detect patients with high-titre circulating TgAb (>4 U/L for the reference range of our laboratory).

2) Percutaneous EA Procedure

Percutaneous EA was performed by two experienced endocrinologists in an outpatient setting, after patients had given written informed consent. Local anesthesia with 2% Lidocaine was used applied to the puncture site and soft tissue around the recurrent tumor. Then, 2-4 cm long, 21-25 Gauge needles attached to a 2-5 mL syringe containing 97% ethanol were used to inject 0.1-1 mL ethanol (per lesion). Ethanol was then injected from the deep and peripheral portion of the recurrent thyroid cancer to the central area, producing a transient hyperechogenic image of the treated area, according to a procedure that has been described by Shin and colleagues.[25] The procedure was then repeated until the entire tumor changed its echogenicity. Additionally, intranodal power Doppler signal was used to evaluate complete collapse of main tumoral vessels and serial injections were used to ensure complete ablation of tumoral tissue, if needed. Upon completion of the EA procedures, patients remained under observation for 30-60' before discharge for possible complications, as persistent pain, voice change or hoarseness or hematoma. During the follow-up period, patients were scheduled for repeated US at 30, 60 and 90 days after each EA procedure, and then every six months. Indications for repeated EA procedures included tumor volume reduction less than 50%, the presence of power Doppler signals (despite a reduction in tumor size) and/or the presence of residual tumor tissue on fine-needle aspiration cytology and/or a Tg determination in FNA washout >1 ng/mL. Conversely, the absence of all of these conditions was considered a successful ablation, and in such case, patients were followed with US every 6 months for at least 2 years, and then yearly, as part of our routine follow-up schedule. For patients with high levels of circulating TgAb, FNA washout measurements included determination of TgAb to exclude possible interferences in Tg assay.

3) Outcomes

Primary outcomes included evaluation of complete response to EA procedures and safety. Complete response to EA was predefined by presence of US-based criteria: volume reduction >50% and absence of intranodal power Doppler signal; and biochemical criteria: Tg determination in FNA washout <1 ng/mL, all together. Number of EA procedures needed and follow-up duration since last EA procedure were also recorded for each lesion. Safety was evaluated by recording incidence of moderate to severe persistent pain, voice change or hoarseness indicating recurrent nerve injury and US findings as swelling and/or hematoma, after every EA procedure.

A secondary outcome was designed to evaluate impact of EA procedures on disease course. Changes in both plasma TSH-suppressed Tg and TSH-stimulated Tg concentration (when available) were compared pre and post EA procedures. Both baseline plasma TSH-suppressed Tg (closest measurement to recurrence diagnosis) and TSH-stimulated Tg (obtained from last RAI therapy performed before EA) levels were compared to TSH-suppressed Tg and TSH-stimulated Tg performed after last EA procedure, respectively. Last available values for both TSH-suppressed Tg and TSH-stimulated Tg were used for this analysis. Percentage of patients achieving a complete biochemical remission after EA was also evaluated. According to ATA guidelines, a complete biochemical remission was considered for patients with plasma TSH-suppressed Tg concentration <0.2 ng/mL and/or TSH-stimulated Tg concentration <1 ng/mL.[6] In 2015 our Hospital introduced ultra-sensible Tg assay with a limit of detection of 0.04 ng/mL, as compared to pre-

vious method in which limit of detection was 0.2 ng/mL. Since then, less patients not receiving RAI therapy have undergone human recombinant TSH (hrTSH) stimulated Tg determinations, based upon ultra-sensible Tg high sensitivity for detecting recurrent disease. For patients undergoing TSH-stimulated Tg measurement, no differences were taken into account for either use of hrTSH stimulation or tiroxine treatment withdrawal as all patients achieved a plasma TSH value >15 mU/mL for Tg measurements.

Finally, an exploratory outcome was designed to evaluate response to EA and long-term risk of recurrence between patients with high and low risk of new recurrence who would receive or not post-EA RAI therapy, respectively, by evaluation of percentage of successful EA procedures, change in plasma TSH-suppressed Tg levels and development of new recurrences during follow-up for both groups.

Statistical comparative analysis was performed, despite the descriptive nature of this study, for baseline characteristics of lesions and patients who did, or did not undergo post-EA RAI therapy, respectively, and for comparison of frequency of US and biochemical pre-defined criteria of successful EA. Normally distributed variables were expressed as mean±standard deviation (SD) or range and non-parametric variables were expressed as median and 25-75th interquartile range. Two-sided T-student test was used for comparisons of normally distributed variables and Chi-square test was used for comparisons of non-parametric variables.

Results

Baseline Characteristics of Patients

No significant differences were found between both groups of patients (with or without post-EA RAI treatment) in regard of sex distribution or elapsed time from initial surgery to diagnosis of recurrence. Patients assigned to post-EA RAI treatment were older and presented more frequently lateral neck lymph node involvement at baseline, had undergone more frequently rescue surgery and had received higher doses of RAI therapy, as compared to patients who did not undergo post-EA RAI therapy. Ten patients with initial TNM stage I or II were assigned to post-EA RAI treatment because of ≥2 neck compartments with lesions or aggressive PTC histology. A patient with oncocytic variant of FTC who presented with 4 seed metastases on ECM muscle and subcutaneous fat was also assigned to receive post-EA RAI treatment.

Performance of EA Procedures

Table 3 shows performance of EA overall and on each group following or not RAI therapy. A total of 169 EA procedures (mean 2.38 per lesion, 4.02 per patient) were performed over 71 lesions (32 in the No RAI treatment group and 39 in the RAI treatment group), with no differences in number of procedures between both groups, neither per lesion, nor per patient. Ethanol volume injected per lesion and EA procedure was similar in both groups, in accordance with the similar size.

According to US and biochemical predefined criteria for complete response, 87.32% of treated lesions (62 of 71) were successfully ablated with no differences between both groups (34/39 in the RAI treatment group, and 28/32 in the No RAI treatment group). A volume reduction of 84.82±26.10% versus baseline volume was achieved, again without differences between both groups of patients (83.32±24.52% in the post-EA RAI treatment group, and 86.66±28.04% in the No RAI treatment group). Lesion volume reduction >50% was more frequently achieved (97.18%, 69/71 lesions) as compared to loss of power Doppler signal (87.32%, 62/71 lesions) or FNA washout Tg <1 ng/mL (91.54%, 65/71 lesions), ($p<0.05$, for both comparisons). Of note, volume reduction >50% was achieved by 69% of treated lesions following 60 days after initial EA as compared to 60.7% and 61.4% of lesions achieving complete loss of Doppler signal or washout Tg value <1 ng/dL, respectively. By six months of follow-up, most successfully treated lesions had achieved a complete response (60/71). Only two lesions located in the upper mediastinum of a 21-year-old woman with a difficult US-guided access, needed up to 5 sessions and one year of follow-up

Table 3. Percutaneous ethanol ablation (EA) results

	Total	No post-EA RAI treatment	Post-EA RAI treatment
Patients (n)	42	23	19
Number of lesions	71	32	39
Follow-up, months (mean±SD)	40.50±18.01	41.76±19.43	38.65±16.83
Number of EAs	169	74	95
Per lesion (mean±SD)	2.38±1.26	2.31±1.12	2.43±1.31
Per patient	4.02	3.21	5.0
Ethanol volume			
Per procedure, mL (mean±SD)	0.82±0.65	0.80±0.58	0.84±0.75
Per lesion, mL (mean±SD)	1.95±1.32	1.85±1.15	2.04±1.44
Volume reduction (%) (mean±SD)	84.82±26.10%	86.66±28.04%	83.32±24.52%
Lesions with >50% volume reduction, % (n)	97.18% (67)	96.87% (31)	97.43% (38)
Lesions with loss of Doppler signal, % (n)	87.32% (62)	87.5% (28)	87.17% (34)
Lesions with Tg<1 ng/mL in FNA washout, % (n)	91.54% (65)	93.75% (30)	89.74% (35)
Lesions with full response[¶], % (n)	87.32% (62)	87.5% (28)	87.17% (34)
Lesions completely disappeared, % (n)	67.60% (48)	71,87% (23)	64,10% (25)
Recurrent EA treated lesions, % (n)	5.63% (4)	3.12% (1)	7.69% (3)
New recurrent disease in EA treated patients % (n)	16.66% (7)	8.69% (2)	26.31% (5)*
% patients with adverse events			
Moderate to severe persistent pain % (n)	30.95% (13)	26.08% (6)	36.84% (7)
Transient recurrent nerve injury % (n)	7.14% (3)	4.34% (1)	10.52% (2)

FNA: fine needle aspiration, RAI: radioactive iodine, SD: standard deviation
[¶]A successful EA procedure was considered when all >50% volume reduction, loss of Doppler signal and Tg <1 ng/dL in FNA washout were achieved in each treated lesion.
*$p<0.05$ (Chi-square test)

to achieve a complete response. Of note, 48 of 71 lesions (67.6%) were not identifiable in subsequent US studies, either due to complete disappearance or substitution by scar tissue. No differences were seen for patients receiving or not post-EA RAI therapy in this proportion (64.1% vs. 71.8%, respectively). For the remaining lesions identifiable at serial US studies, FNA cytology was performed at least once to rule out persistence of tumor. As stated, FNA washout Tg <1 ng/mL and additionally, absence of cellularity in FNA smears were considered a positive response. Of 23 identifiable lesions, 9 lesions presented an FNA washout Tg >1 ng/mL, 5 of them with a positive cytological diagnosis of malignancy and in the remaining 9, FNA washout Tg was <1 ng/mL. Of note, for 3 of these patients, the pathologist reported on normal lymph node cytology with absence of tumoral cellularity in FNAs performed on identifiable lymph node metastases after successful EA procedures, raising the hypothesis of a possible restoration of normal lymph node architecture after EA.

Overall, EA procedures were conducted safely with few reported adverse events. Moderate to severe persistent pain, ranging from hours to days after EA sessions, was present in one third of patients, with a higher proportion of patients in the RAI treatment group, probably because of a higher number of paratracheal thyroid bed or region VI lesions in these patients, although it was effectively managed with analgesic medication and local measures in all affected patients. Only three patients presented with transient voice change or hoarseness after an EA procedure, compatible with transient inferior laryngeal recurrent nerve injury, confirmed by laryngoscopy. Two of them had thyroid bed recurrences and a very lean 38-year-old female patient with a single pre-tracheal lymph node, persisted with hoarseness despite treatment with a 10 days course of oral steroid treatment, although it gradually remitted after two months.

Most EA lesions persisted with complete response throughout a mean (range) of 40.50 (12-73) months of follow-up. Only one lesion in the No RAI treatment

group and three lesions from two different patients in the RAI treatment group showed regrowth on US with FNA washout Tg value >1 ng/mL and/or positive cytology for malignancy after full response to previous EA. Furthermore, 7 patients with previous successfully treated lesions presented with new recurrent neck disease in a different anatomical location throughout follow-up. Interestingly, these new lesions were found in up to 5 patients (26.31%) in the RAI treatment group, as compared to only 2 patients (8.69%) in the No RAI treatment group. Four of these patients, all in the RAI treatment group were submitted to rescue surgery on the basis of the number of lesions detected or inability to perform a successful EA procedure, and 3 patients, from both groups, underwent new EA procedures.

Impact of EA Procedures on Systemic Disease

After excluding 4 patients with positive antithyroglobulin antibodies from analysis, Table 4 shows impact of EA on clinical course of disease for patients with[22] and without[16] post-EA RAI treatment, measured by changes in plasma Tg measurements.

In line with inclusion criteria, patients assigned to RAI treatment had significantly higher baseline plasma TSH-suppressed Tg levels (4.34; 2.3-14.48 ng/mL, median; interquartile range), as compared to patients who did not undergo post-EA RAI treatment (1.61; 0.69-4.02 ng/mL, $p<0.05$). Conversely, TSH-stimulated Tg levels, measured when patients initially received post-surgery ablative RAI therapy, were significantly higher in the RAI treatment group (50.84; 13.83-97.7 ng/mL vs. 11.9; 2.82-37.4 ng/mL, $p<0.05$). Last measured plasma TSH-suppressed Tg throughout follow-up, dropped to 0.77; 0.12-4.3 ng/mL in the No RAI treatment group, as compared to 1.43; 0.10-8.1 ng/mL in the RAI treatment group ($p<0.05$). Only four patients who did not undergo post-EA RAI therapy had a hrTSH-stimulated Tg determination. All these patients underwent this test before ultra-sensible Tg assay was available at our institution. As expected, patients in the No RAI treatment group presented a significantly lower TSH-stimulated Tg as compared to patients in the RAI treatment group (1.13;

Table 4. Impact of percutaneous ethanol ablation (EA) on systemic disease for patients with and without post-EA radioactive iodine (RAI) treatment

	Total	No post-EA RAI[†] treatment	Post-EA RAI treatment
Number of patients[f]	38	22	16
Follow-up, months (mean/range)	40.50 (12-73)	41.76 (12-73)	38.65 (15-62)
TNM stage I or II n (%)	19 (50%)	21 (95.45%)	10 (62.5%)
Patients with ≤2 lesions n (%)	15 (39.47%)	17 (77.27%)	8 (50%)
Patients with TSH-supressed Tg<0.2 ng/mL before EA (n/%)	5 (13.15%)	4 (18.18%)	1 (6.25%)
TSH-supressed Tg before EA, ng/mL (median, interquartile range)	2.75 (1.3-9.35)	1.61 (0.69-4.02)	4.34 (2.3-14.48)*
TSH-stimulated Tg before EA, ng/mL (median, interquartile range)	28.28 (6.54-71.0)	11.9 (2.82-37.4)	50.84 (13.83-97.7)*
TSH-supressed Tg after EA, ng/mL (median, interquartile range)	0.85 (0-8.06)	0.77 (0.12-4.3)	1.43 (0.10-8.1)*
TSH-stimulated Tg after EA, ng/mL (median, interquartile range) (n)[α]	11.86 (1.13-30.6) (20)	1.13 (0.93-2.82) (4)	14.68 (1.13-36.33) (16)
Time (months) from EA to RAI/hrTSH (mean±SD)	6.38±5.22	6.15±4.74	6.72±5.83
Patients with TSH-supressed Tg<0.2 ng/mL (n/%)	17/38 (44.73%)	10/22 (45.45%)	7/16 (43.75%)
Patients with TSH-stimulated Tg<1 ng/mL (n/%)	6/20 (30%)	2/4 (50%)	4/16 (25%)

hrTSH: human recombinant TSH stimulation test, SD: standard deviation
[f]Patients with positive thyroglobulin antibodies (4) were excluded.
[†]RAI: Radioactive iodine. α=p not significant. β=p<0.05 (comparison between both groups)
[α]Only four patients underwent hrTSH-stimulated Tg determination without RAI treatment.
*p<0.05 (two-sided t-Student)

0.93–2.82 ng/mL vs. 14.68; 1.13–36.33 ng/mL, $p<0.05$).

Finally, up to 30% of patients remained with complete biochemical remission throughout follow-up, and 44.73% (17/38) of them maintained a TSH-suppressed Tg <0.2 ng/mL, with no differences between both groups.

Discussion/Conclusion

In this descriptive prospective study, we have evaluated the efficacy and safety of US-guided percutaneous EA performed in our institution, in a series of patients with neck thyroid cancer recurrent disease. Predefined combined US and biochemical criteria were used to consider a successful EA procedure, and serial EA sessions were carried out as needed, until lesions achieved complete ablation. Additionally, patients were initially divided into two groups according to initial risk of recurrence measured by TNM stage, need of previous rescue surgery and tumoral load based upon number of lesions and plasma Tg levels; those with lower risk and low tumoral load would not undergo RAI treatment after completion of EA, as opposed to those with higher risk TNM stages, number of lesions or baseline plasma Tg levels who underwent additional post-EA RAI ablation therapy. Upon completion of AE procedures, plasma TSH-suppressed and TSH-stimulated Tg levels (when available) were measured when clinically indicated during follow-up, and results were compared to baseline values to asses impact of EA with and without RAI therapy on disease course. Furthermore, recurrence of treated lesions and new neck recurrences were recorded for patients on both groups during follow-up. Of note, all EA procedures were performed with local anaesthesia in an outpatient setting and patients were discharged after an observation period of 30 to 60 minutes.

Patients included in this study predominantly had a low postoperative TNM stage with a histology of PTC, not surprisingly, as these patients are more likely to be selected for local procedures as an alternative to rescue surgery. Patients with more advanced TNM stages at the time of initial surgery or more aggressive histologic types were included in this study either because of low tumoral burden with low serum Tg concentration, or high-risk surgery or patient's preference. Of note, up to 13 patients (30.95%) had undergone previous rescue surgery, and in most cases, this surgery had taken place before EA procedure was available at our institution. Additionally, most recurrent lesions detected were small (average volume less than 0.5 cc) and located in the III-IV lateral neck compartment, whereas up to 22% of lesions recurred in the thyroid bed, were rescue surgery is associated to a higher risk of recurrent nerve injury due to scar tissue. No meaningful differences were seen regarding age, sex distribution or time from surgery between patients in the RAI versus No RAI treatment groups. Conversely, patients assigned to receive post-EA RAI therapy harboured more advanced tumors with more frequent need of rescue surgery and had received previously higher doses of radioiodine. As stated before, all patients were included in this study after approval by a multidisciplinary committee composed by endocrinologists, surgeons and Nuclear Medicine specialists.

Efficacy and safety of EA was the main outcome of this study. Overall, EA showed a high rate of success, with 87.32% of lesions completely ablated after initial EA procedures and a very low rate of relapse (5.63%) of ablated lesions, so that by the end of follow-up, 81.69% of treated lesions remained successfully ablated. Of note, up to 32.4%[23] lesions did not completely disappear in subsequent US studies, despite fulfilling predefined US criteria of >50% volume reduction. It is important to note that the lack of complete involution of treated lesions does not imply treatment failure, as has been stated in different consensus reports on image-guided thyroid tumor ablation.[32,33] The new recurrent neck disease observed throughout follow-up (16.66% of patients), is low and coincides with previously reported series, even with a longer follow-up.[34-36] In general, response to EA was similar for both groups of patients undergoing or not post-EA RAI treatment, indicating a homogeneous initial response to the procedure regardless of risk of recurrence. Nevertheless, risk of new recurrences was higher in the higher risk group (26.31% vs. 8.69%), supporting the need of post-

ethanol RAI therapy in these patients.

Overall, EA procedures were conducted safely and with few adverse events. Moderate to severe pain beyond EA procedure affected transiently to one third of treated patients, and only three cases were described of transient voice change or hoarseness. This low rate of complications is in line with previously reported results, where transient pain or regional discomfort can virtually affect to 100% of treated patients. Incidental voice change due to inferior laryngeal nerve injury is reported as low as 2.7% of treated patients, most of them recovering in the following days to weeks.[35]

A secondary objective of this study was to evaluate EA impact on systemic disease as reflected by changes in plasma circulating Tg throughout follow-up. Notably, 44.73% of patients achieved a TSH-suppressed Tg <0.2 ng/mL after EA, and for patients who did not undergo subsequent RAI ablation therapy, this result reflected the solely effect of ethanol. Nevertheless, this percentage dropped to 25% in the RAI treatment group when TSH-stimulated Tg was taken into account. The small number of patients undergoing hrTSH-stimulated Tg determinations in the No RAI treatment group does not allow for comparisons between both groups. Despite post-EA RAI therapy was arbitrarily selected based upon clinical features, i.e. postoperative TNM stage, histology of primary tumor, number of lesions and circulating levels of Tg before EA, the percentage of patients with TSH-suppressed Tg was similar between both groups and even more, the risk of new neck recurrences was lower for patients not undergoing RAI therapy (8.69% vs. 26.31%, respectively), perhaps indicating that a subgroup of patients with low risk of new recurrences, may benefit from just active surveillance after successful EA. Indeed, local recurrence following EA occurs in 3.2-33% of treated patients[35] and our data coincides with this previously reported range, but with a clearly lower risk in selected patients not receiving post-EA RAI therapy. Kim et al.[36] reported that risk of new recurrence was higher among older patients and curiously, in those with smaller lymph node size. In our series, patients with new recurrences were older, had bigger treated lymph nodes and followed post-EA RAI treatment based upon their higher risk.

A recent review has evaluated published series of patients with thyroid cancer recurrent neck disease who underwent EA.[35] Despite heterogeneous variables were described in regards of EA results, 70-98% of patients achieved a 50% or greater volume reduction and 31-46% achieved complete disappearance of treated lesions. Besides, some of these studies showed comparison between plasma thyroglobulin levels before and after EA, showing a marked descend in 50-55% of treated patients. Hay et al.[22] reported that 12 of 22 patients remained on long-term biochemical remission after EA, and Heilo et al.[21] reported that 30 of 38 patients with detectable serum thyroglobulin before EA, achieved undetectable (<0.2 mcg/L) serum thyroglobulin levels after 38 months of average follow-up. None of these authors reported on RAI therapy or TSH stimulated Thyroglobulin levels following EA. Recurrence of neck disease following EA procedures has been described in the range of 25-35%, with risk being higher for older patients with higher levels of circulating thyroglobulin or number of lesions treated.[36,37] Kim et al.[36] described a recurrence rate after EA as low as 17.1% after a mean follow-up of 81 months in a series of 29 patients, based upon increased size of previously treated lesions, indicating that the procedure is effective in the long term. Of note, after a classic strategy of surgical reintervention of neck recurrent disease, followed by RAI therapy, only 30-51% of patients achieve structural and biochemical remission.[15-17] Several authors have compared surgical reintervention versus EA. In 2015, Fontenot et al.[38] published a systematic meta-analysis concluding that reintervention was superior to EA (94.8% vs. 84.5% rate of success, $p<0.01$), although only 11% of patients in this meta-analysis underwent EA. Additionally, rate of complications was higher for patients who underwent surgery (3.5% vs. 1.2%). These results are quite similar to those obtained in our present study. In this setting, image-guided ablation techniques have the attraction of being accurately delivered without the need for general anaesthesia and complications, including postoperative haemorrhage and permanent damage to the recurrent laryngeal

nerve associated with surgery, make a minimally invasive approach more attractive. Furthermore, in addition to potential clinical benefits, EA is usually performed in outpatient settings and therefore, this approach allows for significant costs savings.[24)]

Conversely, active surveillance of US detected lymph node metastases of PTC may be an appropriate approach for selected patients taking in mind that many lymph node recurrences may remain stable for a long time and not be immediately life-threatening. Tomoda et al.[39)] followed 83 patients with PTC with at least one lymph node confirmed recurrence for a median follow-up of 7.2 years. Serial US studies showed a median growth rate of the nodes showing structural progression of 1.4 mm per year, and interestingly, in up to 39.7% of patients, detected lymph nodes spontaneously resolved without further treatment. In this study, a growth rate of 3 mm or more per year was independently associated to reduced survival. In this setting, only 20.5% of patients (those with a groth rate ≥3 mm per year) would deserve active management (either a percutaneous technique or surgical lymph node compartment dissection), which again, is comparable to a 16.66% of new recurrences after EA in our study.

A recent meta-analysis by Suh et al.[34)] compared the efficacy and safety of RFA and EA for the management of recurrent thyroid cancers. The paper included a total sample size of 270 patients and 415 lesions and concluded that both RFA and EA were acceptable treatment modalities to manage locally recurrent thyroid cancer in terms of efficacy and safety for poor surgical candidates or those who refuse surgery. Pooled proportion of volume reduction >50% was 100% for RFA and 89.5% for EA, with a lower number of RFA sessions (<1.3) as compared to EA (>2), and pooled proportion of recurrence was 0.0% and 2.4%, respectively, although differences did not reach statistical significance. Conversely, pooled proportion of serum Tg reduction was 71.6% for RFA and 93.8% for EA ($p<0.001$), although this difference is probably reflecting a higher complexity of patients undergoing RFA. Finally, pooloed proportion of complications was low, and similar between the two techniques; 1.6% after adjustment for both.

Two papers have explored the feasibility and results of an alternative minimally invasive rescue surgery for patients with loco-regional recurrence from DTC using Radioguided occult lesion localization (ROLL) combined with US preoperative mapping.[40,41)] Nevertheless, while US-guided radiolabelled material intralesional injection can help in detecting US-occult lymph node involvement, a 33 to 40% recurrence rate has been reported with this technique, similar to classical neck disecction reported recurrence rates.

Our study has several limitations, most of them derived from its descriptive nature. First, the lack of a matched control group does not allow to compare EA to other strategies, like active surveillance or rescue surgery, on rates of success, comorbidity or impact of interventions on systemic disease. Second, a median follow-up of 40.5 months cannot be considered a long-term observation period in the context of the natural history of DTC, but we consider it is a reasonable period of time to ensure successful ablation of targeted lesions. Else, distinction between patients who did or did not undergo RAI treatment was arbitrary and based upon clinical criteria, thus a comparison between both groups in terms of long-term risk of recurrence is clearly biased. Nevertheless, the intention of this distinction was to explore whether a low risk group of patients could benefit from active surveillance rather than RAI therapy after EA. Indeed, both groups responded equally to EA procedures, but lower risk patients who did not undergo RAI therapy presented a very low rate of new recurrences, giving thus support to this hypothesis. On the other hand, our study has some strengths: first, our data robustly coincides with previously published results of EA for neck recurrent thyroid cancer, in terms of efficacy, adverse events and overall rates of recurrence, providing that the procedure, performed by different groups worldwide is reliable and safe. Second, we have extensively detailed US and biochemical criteria used to define a successful ablation, aiming to introduce a standardized definition of EA procedure. Furthermore, impact of EA in systemic disease is clinically significant, as reflected by the percentage of patients

who achieved biochemical remission, and according to published data, not significantly different from rescue surgery in terms of risk of recurrence for this selected population.

Finally, despite advances in this field, few centres offer US-based percutaneous therapies and currently, there are no definitive guidelines on how EA should be selected and used to treat locally recurrent thyroid cancer. Therefore, it is timely and necessary to collect new data as much of the currently available evidence has been provided by a small number of motivated groups with extensive experience.[24,34,35] While large, randomized prospective studies may not be feasible for evaluation of every new intervention, adherence to a rational treatment protocol may allow for a relatively easy retrospective comparison to standard of care. In this sense, in our study we have carefully predefined criteria for successful response to ablation procedures and correlated to risk of new recurrences.

In conclusion, despite rescue surgery remains as the standard of care for patients with DTC neck recurrent disease, our study shows in alignment with previous studies, that US-guided percutaneous EA is a cost-efficient (as compared to surgery), safe and highly effective method to control neck recurrences of thyroid cancer with a positive impact on systemic disease and with similar results to rescue surgery in selected patients. Additionally, despite adjuvant RAI therapy is advoked for patients with structural evidence of disease after rescue surgery or percutaneous procedures, our study raises the hypothesis that for selected low-risk patients, active surveillance rather than RAI therapy can be an acceptable strategy with low risk of further recurrence. Probably, the time has come to explore the potential of ethanol and other percutaneous techniques in the management of recurrent thyroid cancer disease in the setting of prospective long-term controlled trials. Until then, a standardised universally accepted protocol for this technique, including criteria for patient selection, clear definitions of successful ablation procedures and the role of subsequent RAI therapy for selected patients is highly recommendable.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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