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Clinical Research Article

Can Ethanol Ablation Achieve Durable Control of Neck Nodal Recurrences in Adults With Stage I Papillary Thyroid Cancer?

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Abstract

Objective: Results of ethanol ablation (EA) for controlling neck nodal metastases (NNM) in adult patients with papillary thyroid carcinoma (APTC) beyond 6 months have rarely been reported. We now describe outcome results in controlling 71 NNM in 40 node-positive stage I APTC patients followed for 66 to 269 months.

Methods: All 40 patients were managed with bilateral thyroidectomy and radioiodine therapy and followed with neck ultrasound (US) for >48 months after EA. Cumulative radioiodine doses ranged from 30 to 550 mCi; pre-EA 27 patients (67%) had 36 additional neck surgeries. Cytologic diagnosis of PTC in 71 NNM selected for EA was confirmed by US-guided biopsy. EA technique and follow-up protocol were as previously described.

Results: The 40 patients had 1 to 4 NNM; 67/71 NNM (94%) received 2 to 4 ethanol injections (total median volume 0.8 cc). All ablated 71 NNM shrank (mean volume reduction of 93%); nodal hypervascularity was eliminated. Thirty-eight NNM (54%) with initial volumes of 12-1404 mm^3 (median 164) disappeared on neck sonography. Thirty-three hypovascular foci from ablated NNM (pre-EA volume range 31-636 mm^3; median 147) were still identifiable with volume reductions of 45% to 97% observed (median 81%). There were no complications and no postprocedure hoarseness. Final results were considered to be ideal or near ideal in 55% and satisfactory in 45%. There was no evidence of tumor regrowth after EA.

Conclusion: Our results demonstrate that for patients with American Joint Committee on Cancer stage I APTC, who do not wish further surgery or radioiodine, and are uncomfortable with active surveillance, EA can achieve durable control of recurrent NNM.

Key Words: PTC, adults, ethanol ablation. nodal metastases, outcome

Abbreviations: AJCC, American Joint Committee on Cancer; APTC, adult papillary thyroid carcinoma; ATA, American Thyroid Association; DTC, differentiated thyroid cancer; EA, ethanol ablation; MIT, minimal invasive therapy; NNM, neck nodal metastases; PI, principal investigator; PTC, papillary thyroid carcinoma; pTNM, postoperative tumor–node–metastasis; RFA, radiofrequency ablation; RRA, radioiodine remnant ablation; RLN, recurrent laryngeal nerve; US, ultrasound; Tg, thyroglobulin; TST, thyrotropin-suppressive therapy; WBS, whole body scan.

Despite potentially curative bilateral thyroidectomy, extensive nodal resection and postoperative radioiodine remnant ablation (RRA), persistent or recurrent papillary thyroid carcinoma (PTC) in the experience of the Mayo Clinic during 1960-2019 was discovered in regional (neck) nodes in 10% to 15% of adult patients with PTC (APTC) (aged 19-54 years at presentation) within 20 postoperative years [1-3]. Historically, these persistent or recurrent neck nodal metastases (NNM) have been treated by further radioiodine treatments or secondary neck exploratory surgeries; such surgical procedures, unfortunately, are often associated with increased risk of recurrent laryngeal nerve (RLN) or parathyroid gland injury [4].

In 2021 the European Thyroid Association clinical practice guidelines [5] recommended minimally invasive therapies (MITs) as an alternative option to surgical neck redissection in "patients with radioiodine refractory cervical recurrences who are at surgical risk or decline further surgery." In 2022 an American Association of Clinical Endocrinology disease state clinical review [6] concluded that "encouraging results suggest that minimally invasive techniques can also be used in small-size primary and locally recurrent thyroid cancer." Additionally, an international expert panel organized by the American Head and Neck Society Endocrine Surgery Section on behalf of 8 National and International Associations recently approved [7] ethanol ablation (EA) as a "suitable first-line therapy" for NNM in patients with APTC.

At the Mayo Clinic we first employed EA for the control of NNM in differentiated thyroid cancer (DTC) in 1991 [8] and by 2023 we had employed EA in APTC for more than 3 decades. We and others [9, 10] have demonstrated the long-term efficacy of this MIT in APTC, and, moreover, in 2020 we demonstrated that in a single patient with APTC the technique can be repeated on at least 8 occasions to eliminate neck nodal

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disease [11]. Durability of local control beyond 60 months by EA has rarely been reported in patients with APTC [10]. In this present study, we describe outcome results of EA in controlling 71 recurrent NNM in 40 patients with American Joint Committee on Cancer (AJCC) postoperative tumor–node–metastasis (pTNM) stage I [12] APTC now followed on average for 14 years since first EA.

Materials and Methods

Details of the Ethanol Ablation Procedure

All EA procedures for controlling NNM in stage I APTC during 2001 to 2017 were performed by 3 staff radiologists (R.A.L., C.C.R., and J.W.C.) who by 2001 had a collective experience of more than 50 years at Mayo Clinic in sonography and ultrasound (US)-guided interventions. The sonography scanner and the transducers used were as previously described [11, 13]. Each NNM was carefully measured and the pretreatment volume (in millimeters cubed, mm^3) calculated using the ellipsoid formula [14] of anteroposterior × transverse × longitudinal diameters × 0.52. Color Doppler ultrasonography was performed to document presence and degree of intratumoral perfusion. The ethanol injection technique was based on the procedure used at Mayo since 1988 to treat selected parathyroid adenomas [15] and as reported initially for NNM elimination by Lewis and colleagues in 2002 [16].

The patients with APTC had ablation performed soon after biopsy-confirmed positive cytology; injections were typically performed in 2 sessions on successive days as an outpatient procedure under local anesthetic. The tumoral volume and vascularity of the treated NNM was documented in the first and all subsequent sonographic reports.

The volume of injected 95% ethanol was chosen by the treating radiologist at the time of each ablative session. No formula was used to calculate the volume of injected ethanol. Prior to EA, it was explained to the patient by both the endocrinologist and the radiologist performing the ablative procedure that further radioiodine therapy or neck re-exploration would be the traditional therapy for NNM but that, based on extensive experience at Mayo since 1991 of successfully controlling and often completely eliminating NNM in APTC [4, 8, 9, 11, 16], EA represented a very acceptable alternative. However, it was also explained that EA would likely control or eliminate the biopsy-proven NNM but, in itself, could not prevent a very low risk of future locoregional recurrence in other cervical compartments. The treating radiologist prior to intervention obtained signed informed consent from all 40 patients with APTC selected for EA.

Institutional Review Board Approval of Study

The study of ablated patients was approved initially by the Mayo Clinic Institutional Review Board in January 2007 and most recently had its annual update as Study Protocol ID# 13-000319 on January 15, 2024. All patients gave permission for their clinical and sonographic data to be included in the present study.

Follow-up Protocol

Routinely, the study patients were asked to return 3 to 4 months after the initial EA sessions for a recheck examination. At that visit, the patient would be assessed by the treating endocrinologist (I.D.H.) and, whenever possible, the sonographic images were carefully reviewed by the radiologist who performed the initial ablative procedure. The ablated NNM would be carefully remeasured and the volume compared with the preablation value. Doppler flow would be reassessed and consideration given to the need for a further ethanol injection. In general, further injections would be considered if Doppler flow was not completely eliminated. When flow was eliminated, the maximum diameter and the volume of the ablated NNM had typically decreased. Subsequently, patients would return for reassessment 1 year after EA and thereafter, if possible, annually until stability of volumes was achieved or the ablated NNM disappeared.

At each follow-up visit after ablation the sonographer would create for the radiologist's report an annotated nodal map of the neck as well as providing for each ablated nodule the anteroposterior, transverse, and longitudinal diameters and calculated nodal volume at 3 time points: prior to first ablation, at last visit preceding the present follow-up, and on the latest date of sonographic examination. After disappearance of the ablated focus or volume stability in still identifiable lesions, the interval between return visits would be increased to 18 months and eventually to 24 months.

At the time of latest follow-up, only 16 (40%) of the patients at a median follow-up of 166 months (13.8 years) were still being followed at Mayo Rochester, and during that period they had undergone a median of 12 diagnostic neck sonograms and 8 care episodes (range 3-26) supervised by the principal investigator (PI). The other 24 (60%), after a median of 163 months (13.6 years) post-EA, were being followed by local physicians, had undergone at Mayo Rochester a median of 11 diagnostic neck sonograms and 11 care episodes (range 4-20) supervised by the PI. For this study the medical records from Mayo Clinic, and, where indicated, those of the local physicians, were reviewed during January through August 2023 by the PI (I.D.H.) and, when indicated, follow-up obtained directly from the patients themselves. All neck sonograms performed on the 40 ablated patients at the Mayo Clinic were reviewed for this study by our most experienced interventional sonographer (R.A.L.) who personally during April to June 2023 remeasured the volumes of each of the 71 NNM, estimated the volumes of injected ethanol injected, reassessed the Doppler flow in each case, and recalculated the volume reductions achieved by the time of the last follow-up visit.

Results

Initial Management of Patients With AJCC Stage I APTC Selected for EA of NNM

The 40 patients with AJCC stage I (pT1-3N1M0) APTC (25 women, 15 men: median age at PTC diagnosis 28 years, range 19-44 years) included in this study had potentially curative primary surgery (bilateral thyroidectomy and extensive neck nodal resection) performed in 23 different US states during 1985 through 2015. The studied cases were given numbers based on the date of first EA at the Mayo Clinic in Rochester, Minnesota. Thus, case 1 had been treated in July 2001 and case 40 in April 2017. Their postoperative metastases–age–completeness–invasion–size scores [2] had all been in the low-risk category (scores <6) and ranged from 3.4 to 5.6 with a median value of 4.1. The initial T-tumor categories [12] were T1 in 20 (50%), T2 in 13 (32.5%), and T3 in 7 (17.5%). The N-nodal categories were N1a in 24 (60%)

and N1b in 16 (40%). During 2001-2017 all 40 patients had been referred to the Mayo Clinic for tumor surveillance and their care was being supervised by the PI. Prior to attending Mayo, as illustrated by Fig. 1, all had been administered postoperative therapeutic ^{131}I (median cumulative dose of 150 mCi; range 30-550 mCi) and had been demonstrated to have no ^{131}I uptake on whole body scans (WBS). Thus, at time of selection for EA all 40 patients were AJCC pT1-3N1M0 AJCC stage I [12]. Moreover, 27 patients (67%) had 36 additional neck surgeries for neck recurrences; 4 (15%) developing postoperative unilateral vocal cord paresis caused by RLN damage.

All patients selected for study inclusion were required to have no more than 4 biopsy-proven NNM containing PTC and needed to have been regularly re-examined at our institution by neck US to ascertain the completeness of the EA procedure for a minimum of 4 years after initial EA. If further neck dissection was performed during that 4-year period in the neck compartment of the ablated NNM, that patient was no longer eligible for the study. Only 1 such patient, who had EA in 2001 for a right level 4 NNM and had neck re-exploration for previously unrecognized regional disease in 2002, was excluded for this reason from the study. None of the studied patients were included either in our initial 2002 paper on EA in PTC [16] or our previous report [9] of long-term results of EA in 25 patients with advanced localized APTC.

Timing of Presentation, Neck Nodal Metastases Identification, and Selection for Ethanol Ablation

The time interval from initial surgery to consideration of EA of NNM was variable, ranging from as early as 8 postoperative months to as late as 218 months (18.2 years); the median interval was 58 months (4.8 years). Twenty-two (55%) of the 40 studied patients with APTC had their recurrence within 5 years (60 months or less) and were considered to have "early" recurrences (median 35 months; 2.9 years). The other 18 patients had their NNM discovered between 67 and 218 postoperative months; the median interval for these "later" events were 128 months (10.7 years). In the course of clinical evaluations during 2001 through 2017, the 40 study patients were found to have a total of 71 NNM that were confirmed to be metastatic PTC by examination of cytological specimens obtained by US-guided biopsy. Nineteen (48%) patients with APTC had a single NNM, 13 had 2, 6 had 3, and only 2 had 4 NNM selected for EA. All 40 studied patients were evaluated by a multidisciplinary team of Mayo Clinic staff consultants in endocrinology, endocrine surgery, nuclear medicine and interventional sonography who educated the patients regarding the available options to manage the identified and biopsy-proven PTC in NNM. When the 40 patients elected to undergo management with EA, their clinical details were entered prospectively into an institution review board–approved computerized registry of more than 200 patients with differentiated thyroid cancer treated by EA whose care had been supervised by I.D.H. (the PI) since 2001.

Dimensions and Anatomical Locations of 71 NNM Selected for EA

The maximum diameters of the 71 NNM chosen for EA ranged from 4 to 19 mm, and 39 (55%) had maximal nodal diameters less than 1 cm. The median diameter of the biopsy-proven NNM was 9 mm. Volumes of the NNM ranged from 12 to 1404 mm^3 with a median value of 150 mm^3. 44 (62%) had a volume <200 mm^3; 55 (77%) had a volume <300 mm^3. Thirty-four (48%) of the NNM were situated in the central compartment (33 at level VI; 1 at level VII) the other 37 (52%) were in the lateral neck (9 at level II, 12 at level III, and 16 at level IV).

Details of EA Treatment Sessions

At the time of first EA procedure the ages of the 40 patients with stage I APTC ranged between 24 and 47 years (median age 36 years). The 71 selected NNM were treated with a total of 181 ethanol injections. During 2002 and 2007 2 NNM with pre-EA volumes of 150 and 12 mm^3 were successfully treated in cases 7 and 21 with single injections of 0.3 cc. However, the routine practice commencing in 2001 was to inject the ethanol on 2 consecutive days. Of the 71 NNM selected for EA, 45 (63%) with pre-EA volumes ranging from 19 to 636 mm^3 (median 137 mm^3) were adequately treated with a total of 2 injections given on consecutive days; total ethanol volume injected ranging from 0.2 to 1.8 cc (median 0.66 cc). Twelve other NNM (with pre-EA volumes ranging from 31 to 1404 mm^3; median 262 mm^3) had the initial 2-day sessions but also required a third injection at 3 to 6 months (total volume for 3 injections ranging from 0.3 to 2.3 cc; median 0.98 cc) to completely eliminate intranodal blood flow. Additionally, 10 other NNM required a total of 4 injections (total volume 0.55-3.05 cc; median 1.75 cc) performed over a period of 18 to 24 months.

Two exceptional female patients (cases 24 and 27) who were aged 32 and 33, respectively, had their initial EA performed during 2008 and 2010 for single nodes with volumes of 204 and 150 mm and required 8 and 5 injections in 4 and 3 treatment sessions to achieve elimination of intranodal blood flow and significant reduction in nodal volume. Prior to attending Mayo at 80 postoperative months, case 24 had undergone 2 additional neck dissections and moreover had been administered 3 doses of radioiodine for a cumulative dose of 550 mCi given for persistently detectable serum thyroglobulin (Tg) in the absence of demonstrable post-therapy evidence of ^{131}I uptake in the neck. The total ethanol volume given to case 24 was 4.7 cc (the largest total volume administered in this series), the patient achieved a 66% reduction in the initial NNM volume of 204 mm^3, and was last followed up at 170 post-EA months. Case 27 presented to Mayo for EA at 165 postoperative months, having had a second neck dissection and 2 doses of radioiodine for a cumulative dose of 350 mCi, without any post-therapy evidence of neck uptake. She had a total volume of 2.25 cc injected, achieved a 63% reduction in the initial NNM volume of 150 mm^3 and has now been followed for 155 months since first ablation. This result contrasted with case 7 who also had a NNM of 150 mm^3 but after a single injection of 0.3 cc in 2002 his NNM disappeared. Multiple less contrasting cases led us to the conclusion that there was no simple relationship between the reduction in NNM volume achieved and the volume of ethanol injected.

Overall Results of EA in Achieving Control of 71 NNM in 40 Patients with Stage I APTC

Follow-up in the complete study group of 40 patients with stage I APTC, when measured from the date of initial ablation

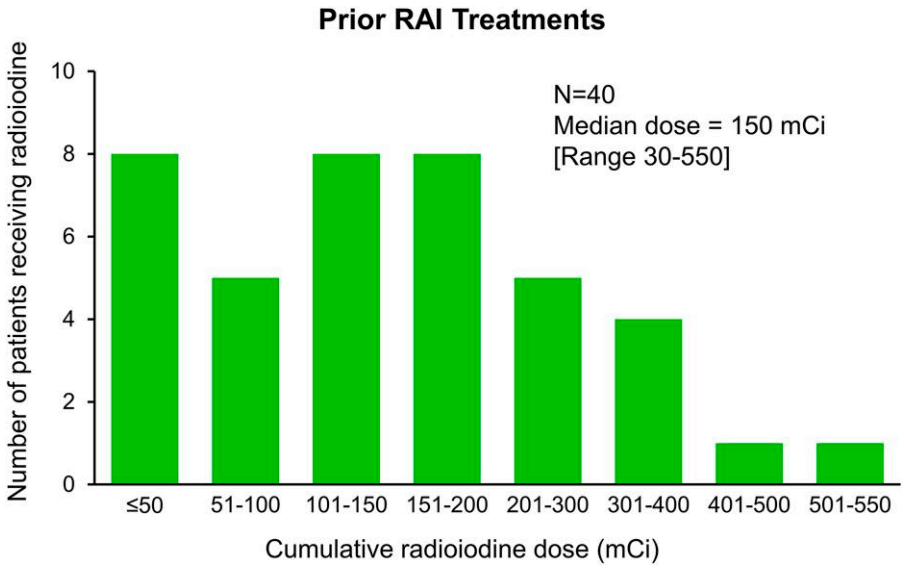

Figure 1. Cumulative dose of therapeutic radioiodine administered to the 40 patients with APTC all of whom received such postoperative treatment during definitive management of their primary diseases. The heights of the 8 columns denote the numbers of patients in each dose category. The dose categories are given on the horizontal axis (30-550 mCi).

to last medical contact, ranged from 66 to 269 months (5.5-22.4 years) with a median follow-up of 14 years. Successful ablation required both reduction in nodal volume and elimination of intratumoral vascularity by Doppler flow measurement. At latest follow-up all 71 NNM selected for EA had experienced a postablation reduction in nodal volume with average shrinkage of 93% and intratumoral vascularity had been eliminated. Thirty eight NNM (54%) had disappeared and were no longer identifiable but all had experienced nodal volume reduction with a median nodal volume shrinkage of 81%. No successfully ablated NNM experienced significant regrowth or required to have subsequent surgical excision.

From a patient's standpoint, the complete disappearance of all ablated NNM represented what was considered to be an ideal result. Such a result was achieved in 16 patients (40%) who had 31 NNM ablated and all disappeared; results were considered "near ideal" in another 6 patients (15%) who had 7 ablated NNM disappear but also had 6 still identifiable avascular NNM which had shrunk after EA on average by 81% to a median volume of 16 mm^3 over a median follow-up period of 149 months (12.4 years). Results were considered to be "satisfactory" if in any one patient all ablated NNM had intratumoral vascularity eliminated and had achieved volume reduction but had not disappeared on repeated sonographic examinations. Such "satisfactory" results were achieved in 18 patients (45%) who had 27 ablated NNM and were treated during 2002 through 2016. Although these patients were followed after successful ablation from 66 to 244 months (median 141 months; 11.8 years), the time taken for the ablated NNM to achieve a stable avascular diminished volume was considerably shorter (median of 11 months and mean of 16 months; range 4-45 months). Figure 2 summarizes the

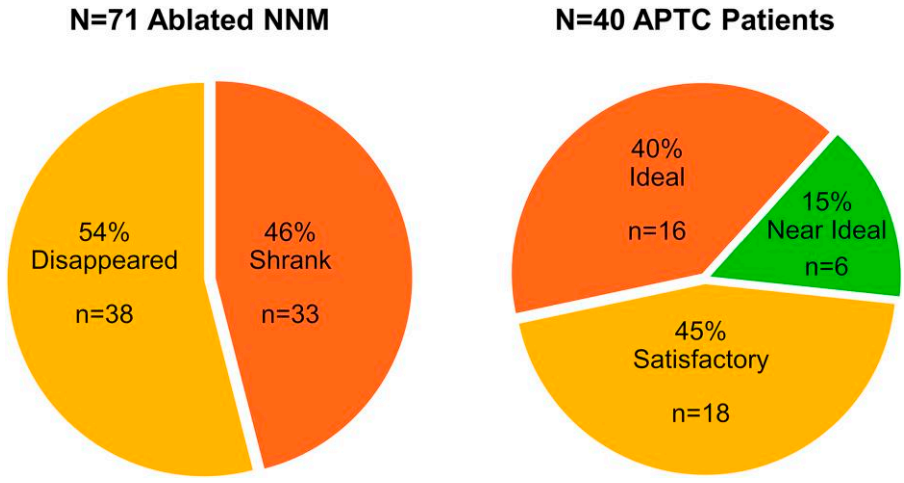

Figure 2. Overall results for EA in stage I APTC for (left panel) 71 ablated nodes and (right panel) 40 patients. For an ideal result, all ablated NNM disappeared; for near ideal each patient had at least 1 NNM disappear and any others shrank after EA. When satisfactory, none of the NNM disappeared but all had reduction in nodal volume and tumor vascularity was eliminated.

overall results as seen from both the 71 ablated NNM and the 40 patients' perspective.

Volume Reduction in 33 Avascular Ablated NNM Still Identifiable on Sonography

At latest follow-up of 141 months (range 66-244) 33 avascular NNM in 24 patients had experienced a median shrinkage of 81% and were still identifiable on neck sonography. The preablation volume of these still identifiable 33 NNM ranged from 31 to 636 mm^3 with a median value of 147 mm^3. The final volume of these 33 shrunken and identifiable NNM ranged from 4 to 166 mm^3 with a median value of 21 mm^3. Figure 3 illustrates the shrinkage by nodal volume in these 33 NNM. When nodal volume was <300 mm^3, the median reduction in the 13 early recurrences (left panel) was 81%, while in the 14 later recurrences (middle panel) it was comparable at 77%. The right panel demonstrates volume reduction data for those 6 NNM whose pre-EA volume exceeded 300 mm^3, there were 2 early and 4 recurrences in this subset and the median volume reduction was 87%. Figure 4 illustrates the range of shrinkage (45-97%) observed in the 33 still identifiable NNM. For the 15 early recurrences (upper panel) the median shrinkage was 79% and median follow-up was 127 months. The lower panel illustrates the comparable range of shrinkage (59-97%) in the 18 still identifiable later recurrences with a median shrinkage of 81% and median follow-up of 141 months. The final median volumes for these avascular 15 early and 18 later recurrences were 19 mm^3 and 31 mm^3, respectively. These final volume results were considered to be "near ideal" in 6 patients with a single identifiable NNM (who also had 7 ablated NNM disappear) and "satisfactory" in the other 18 patients who had 27 ablated NNM. In these 24 patients no more ethanol injections were considered necessary.

Post-EA Disappearance of 37 NNM in 21 Patients With APTC

Preablation, the volumes of the NNM that disappeared after successful EA ranged between 12 and 1404 mm^3 (median 164 mm^3). An ideal result was achieved in 16 patients (40%) whose 31 ablated nodes disappeared; results were near ideal in another 6 patients who had 7 NNM which disappeared but also had 6 avascular NNM, which had shrunk on average by 81% to a median volume of 16 mm^3 on repeated neck sonographic examinations. Figure 5 illustrates the time taken for all 38 NNM to disappear; 25 of 40 NNM (62.5%) considered "early" recurrences (within 5 postoperative years) disappeared at a median of 41 months (range 11-128) after first EA; 13 of 31 NNM (42%) discovered after 5 postoperative years disappeared at a median of 20 months (range 4-69) after first EA. To demonstrate the range of pre-EA volumes of the disappearing NNM the results shown in Fig. 5 represent the maximal nodal volumes for each of the 22 patients with disappearing NNM. For the 12 patients with early recurrences the median maximal nodal volume was 257 mm^3; for the 10 patients with later recurrences the median was 167 mm^3. When pre-EA volume of NNM was 300 mm^3 or less, 29 of 56 successfully ablated NNM (52%) disappeared; when pre-EA volume exceeded 300 mm^3, 9/15 (60%) disappeared after successful ablation.

Possible Predictors of Likelihood of NNM Disappearance After Successful EA

Since the timing of the recurrence and the preablation volume might be relevant to the likelihood of NNM disappearance, the relationship of these variables was further studied. The 71 NNM were divided into 4 groups based on the variables of recurrence timing (before or after 60 postoperative months) and preablation nodal volume (smaller or larger than 300 mm^3). When the recurrence was early and the preablation volume was larger (range 309-1264 mm^3; median value 534 mm^3), the chance of nodal disappearance was 78%. By contrast, the lowest chance of nodal disappearance (33%) was seen when the recurrence was later than 5 postoperative years and the preablation volume was larger than 300 mm^3. The comparable risks for either early recurrences with smaller NNM or later recurrences with smaller NNM were 58% (18/31) and 44% (11/25), respectively.

Changing Serum Tg Levels in 32 Patients Without Tg Antibodies or Lung Micronodules

Six patients had Tg autoantibodies at the time of selection for EA and their Tg autoantibody titers were not serially studied. Two patients (cases 14 and 27) had serum Tg levels of 6.1 and 3.7 ng/mL at time of last follow-up, which were thought, in the absence of persistent neck disease, to be derived from multiple tiny lung nodules seen only on chest computed tomography and never biopsied or visualized by post-therapy ^{131}I WBS.

The serum Tg levels in the remaining 32 patients at the time of first EA ranged from undetectable (<0.1 ng/mL) in 2 patients (with single NNM of 168 and 534 mm^3), through 18 (56%) with levels of 0.1 to 2.2 ng/mL, to higher levels >3 ng/mL (range 3.1-10.0) in 12 (37%). The median serum Tg on thyrotropin-suppressive therapy (TST) pre-EA (n = 32 patients) was 1.9 ng/mL. After EA Tg levels fell in all 30 patients who had detectable Tg before EA. Of 21 patients with pre-EA Tg values of >0.3 ng/mL, who had Tg levels checked within 6 post-EA months, 10 had Mayo rechecks at both 3 and 6 months, 5 at 3 months only, and 6 at 6 months only. For the 15 who had repeat Tg at 3 months, Tg values fell in each case; mean pre-EA Tg was 4.0 and fell at 3 months to 1.5 ng/mL. For the 16 who had a 6 months recheck the pre-EA mean Tg was 3.3 ng/mL and all 16 fell by 6 months; mean Tg at 6 months was 0.9 ng/mL.

At last follow-up serum Tg values in the 32 ablated patients ranged from undetectable to 1.2 ng/mL. Fourteen (44%) had serum Tg levels of 0.1 ng/mL or less; 17 (53%) had levels of 0.2 ng/mL or less. At latest follow-up the median serum Tg level on TST for the 32 ablated patients without Tg autoantibodies or indeterminate pulmonary micronodules was 0.2 ng/mL, a cut-off value on TST recently shown [17] to rule out structural disease in differentiated thyroid cancer with a negative predictive value of 99.9%.

Complications of the EA Procedures

Other than minor neck discomfort typically lasting from 6 to 12 hours after EA, there were no early or late complications attributable to the 181 ethanol injections administered by our 3 staff radiologists. There was no obvious relationship between the degree of neck discomfort and the volume of ethanol injected; rather it was the radiologist's perception that the discomfort perceived was more likely related to the

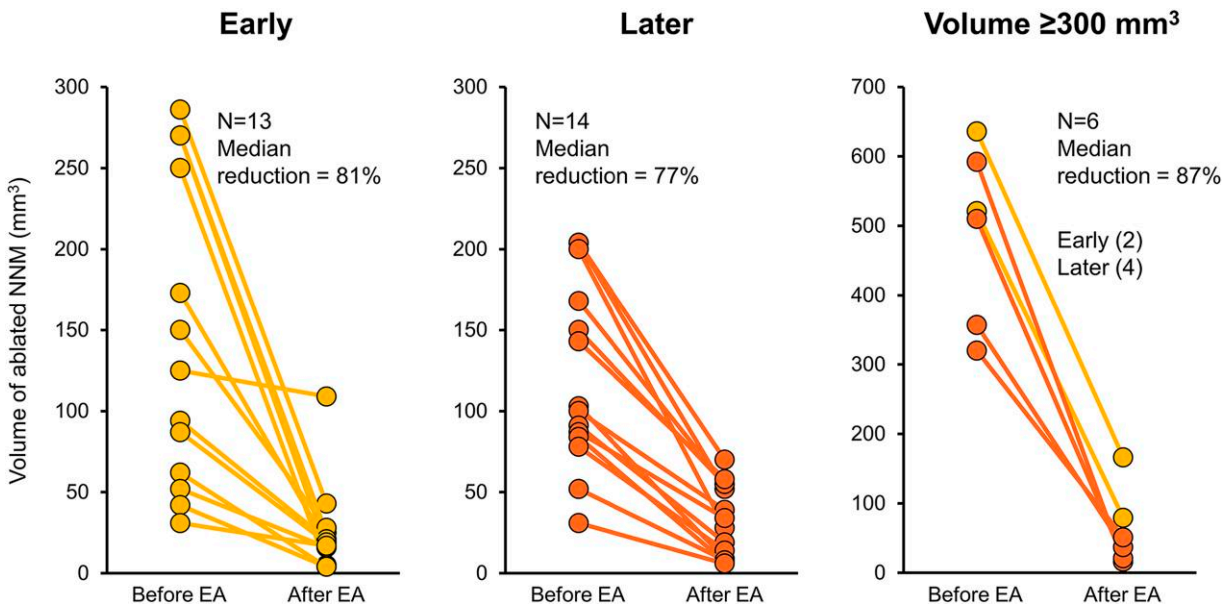

Figure 3. Decreases in volume (shrinkage) in 33 still identifiable NNM. Figures in left panel refer to those 13 early recurrences which had nodal volumes <300 mm^3; figures in middle panel refer to 14 comparable recurrences which occurred later than 60 postoperative months. Right panel illustrates the 6 recurrent nodes (2 early and 4 later) whose volumes exceeded 299 mm^3.

individual patient's acceptable pain threshold. Despite 48% of the ablated NNM being situated within the central compartment of the neck, no example of postprocedure hoarseness was observed in this series, a result likely attributable to the decade's experience at Mayo of EA [8] that preceded the first treatment in 2001 of Patient 1 in this report. Four patients (cases 7, 23, 34, and 40) had iatrogenic unilateral cord paresis prior to EA. Five NNM were ablated in these patients; 1 was located on the same side as the paretic cord, while the other 4 were on the contralateral side and close to the remaining healthy RLN. There was no evidence of any new RLN injury after EA in any of these 4 patients.

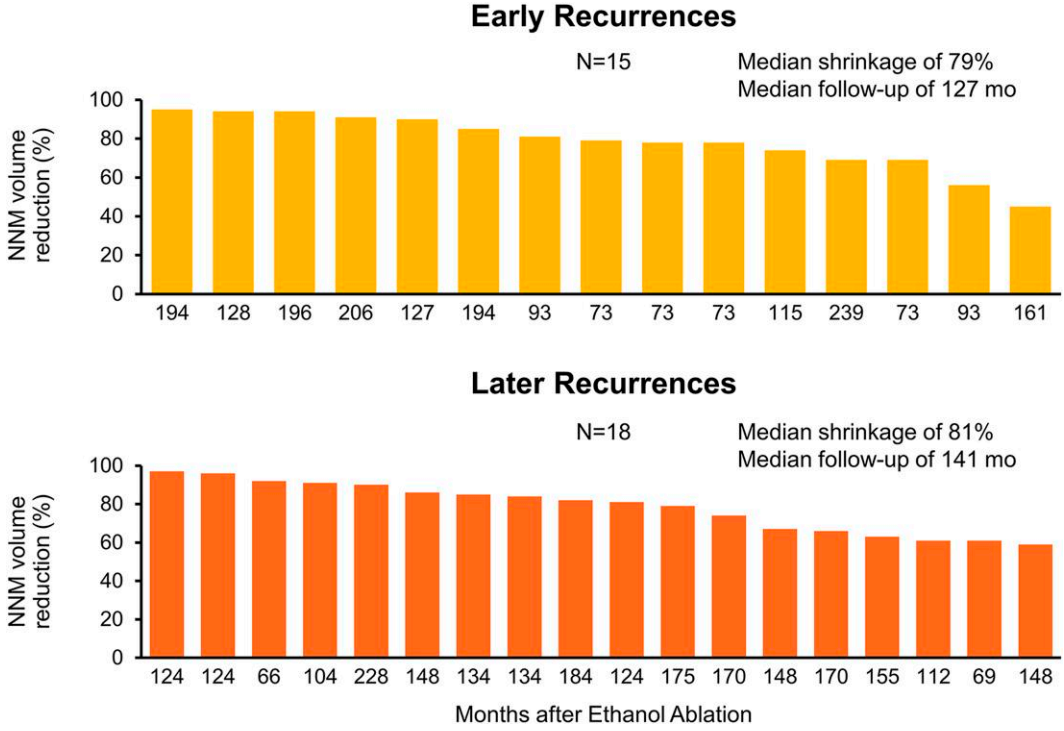

Figure 4. Nodal volume shrinkage in 15 early recurrences (upper panel) and 18 later recurrences (lower panel) observed at last follow-up in 33 still identifiable NNM. The number above each column represents the nodal volume shrinkage observed in an individual ablated NNM. The numbers on the horizontal axis denote the numbers of follow-up months for each ablated NNM.

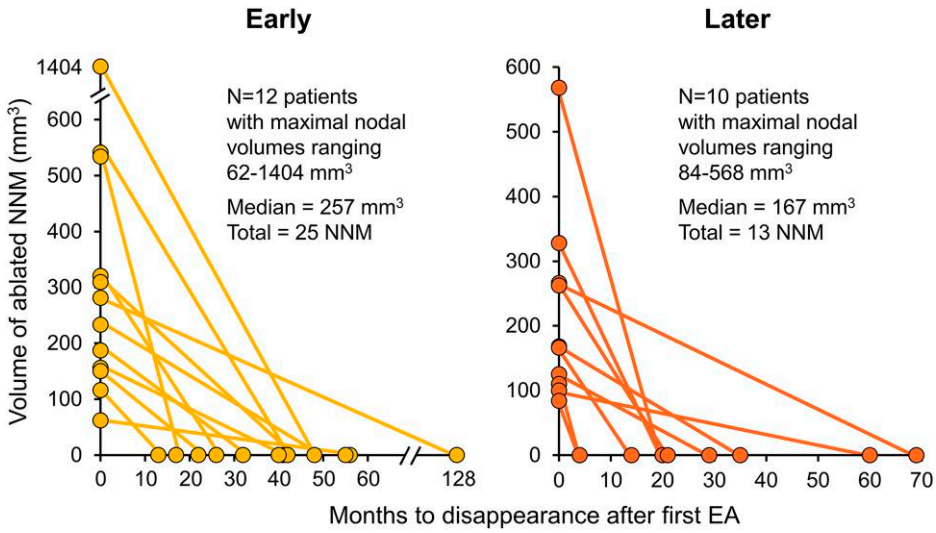

Figure 5. Timing of disappearance of all 38 NNM arranged by preablation volume (vertical axis) and number of months after ablation to disappearance of ablated nodes (horizontal axis) in 12 patients with 25 early recurrences (left panel) and in 10 patients with 13 later recurrences (right panel). For those patients in both panels who had multiple nodes which disappeared, the nodal volume displayed represents the volume of the largest node ablated for each individual patient.

Discussion

During an 85-year period (1935-2019) 4765 patients with APTC had definitive primary treatment performed at the Mayo Clinic in Rochester, Minnesota [3]. During 1935-1939, 75% of these patients presented with AJCC stage I disease [12] but by 2015-2019 this proportion had risen to 88% [3]. Figure 6 (left panel) illustrates the cause-specific survival rates through 20 postoperative years by pTNM staging in the 4765 patients with APTC managed during 1935-2019; only 28 (0.7%) of 4217 stage I patients died due to PTC [3] and cause-specific mortality at 20 postoperative years was 0.8%. Figure 6 (right panel) demonstrates the distribution of patients with APTC managed during 1935-2019 into the four AJCC (8th edition) stages [12], simply represented as 85% with stage I at low-risk of cause-specific mortality and 15% with higher risk (11% with stage II, 3% with stage III and 1% with stage IV disease). At the Mayo Clinic in Rochester, during the past 2 decades the most common reason for the referral of a previously treated patient with stage I APTC to the Division of Endocrinology for further evaluation has been to identify the source of a persistently detectable serum Tg level on TST despite apparently successful thyroidectomy, nodal resection and postoperative RRA and for consideration of EA if the Tg source proved to be a persistent or recurrent NNM potentially amenable to treatment by ultrasound-guided EA.

In December 1993 Goletti and colleagues [18], from Pisa, Italy, first described palliation with percutaneous ethanol injection of an inoperable primary DTC tumor. This tumor was a 21 mm primary PTC in a 75-year-old woman with active pulmonary tuberculosis and congestive heart failure, was found to be "adherent to the trachea but not invading," and "considered unsuitable for operation" [18]. Goletti's group under US-guidance injected "with a 20G needle" twice a week (for 8 sessions) 1 to 2 mL of ethanol directly into the tumor for a total of 14.0 mL of ethanol. Somewhat in contrast to this case of Goletti [18], our multidisciplinary group in May 1993 had treated [8] a 34-year-old woman with stage I PTC who had (despite multiple surgeries, successful RRA and 5400 cGy of external irradiation) a residual 32 mm diameter (1664 mm^3 volume) NNM adjacent to the left carotid bulb and at recent surgery considered to be unresectable. In 3 outpatient sessions this patient received over 10 months a total of 1.4 cc of 95% ethanol by US-guided injection. Her nodal mass shrunk by 94% and at 26 years after successful EA her serum Tg on TST was undetectable, no further disease had been detected and a whole-body positron emission tomography-computed tomography scan showed no focus of fluorodeoxyglucose uptake [8].

In 2015, some 22 years after this first EA of a NNM in APTC, the American Thyroid Association (ATA) Management Guidelines [19] continued to recommend surgery as the optimal directed approach for DTC patients with "biopsy-proven persistent or recurrent disease," particularly for central NNM of >7 mm or lateral nodes of >9 mm. Their consensus on EA for NNM in DTC [19] was that "it may be beneficial in patients with a single or a few metastases, should be considered in patients who are poor surgical candidates, and may require more than one treatment session." They considered [19] that published reports of EA for NNM were limited by small numbers and included many patients whose NNM diameters were <9 mm and who had relatively short follow-up after EA (longest 65 months).

A recently published study from the Oslo University Hospital [10] has managed to address several of the limitations identified by the ATA Guidelines Task Force in earlier studies. In 2022 Frich and colleagues [10] managed to re-examine 44 of the 63 patients with APTC who had previously received EA for selected NNM and had been included in the 2011 study published by Heilo [20]. The median follow-up time from last performed EA was 124 months (range 90-160). Of the 67 initially treated NNM, 97% had fulfilled 1 or more of the defined response criteria at the end of the earlier study [20] and on later follow-up examination 54/67 (81%) had a "durable response," of which the majority (91%) were no longer detectable. Recurrence due to tumor regrowth within a previously ablated node was found in 13/67 NNM (19%) in 10/44 patients (23%); 7 "residual lesions"

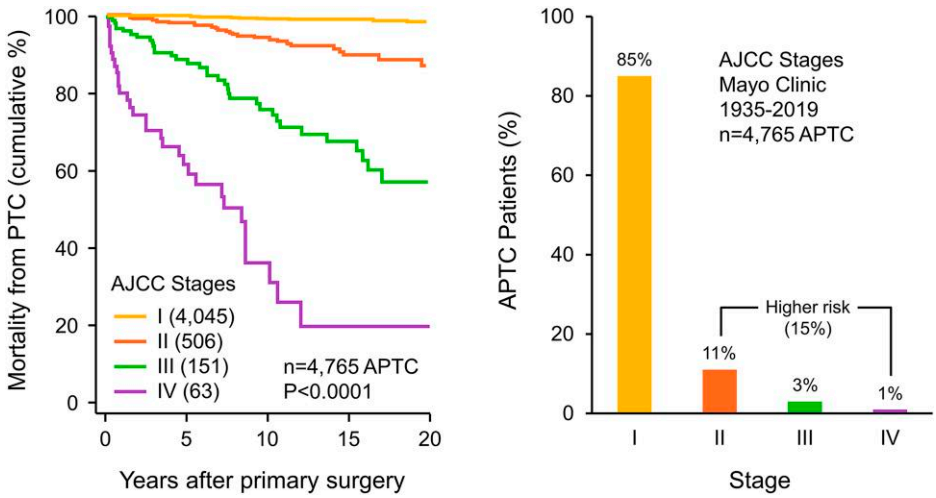

Figure 6. AJCC staging, 8th edition [12], applied to 4765 patients with APTC treated at the Mayo Clinic in Rochester, Minnesota during 1935 through 2019. The left panel demonstrates the cause-specific survival rates seen in stages I, II, II, and IV. The right panel demonstrates the distribution of patients in these 4 stages; the low-risk (of cause-specific mortality) being represented by the 85% in stage I and the higher-risk by the 15% in stages II, II, and IV.

detected during years 6 to 12 (median 9) and 6 at time of follow-up. Seven of these 10 patients also had recurrent NNM elsewhere in the neck. Of the 13 recurrent lesions discovered in previously ablated NNM, 7 were later adequately treated with EA, 4 had reoperative surgery, and 2 underwent active surveillance.

Tumor regrowth at previously ablated sites, reported to occur in from 6% to 24% of ablated nodes (36/249 NNM; mean 14%), represents a new feature of papers published since 2011 [10, 20-24] and certainly warrants further examination. In the 5 identifiable papers describing tumor regrowth in 36 ablated NNM, subsequent treatment details of these NNM were available for only 25. Fourteen (56%) of these 25 NNM, apparently showing "progression," were retreated with further EA while the other 11 underwent RFA, surgery or active surveillance. It is also relevant that in the 2013 study of Guenette [21], where it appears that patients were treated with a single injection of ethanol, the so-called "re-recurrences" [25] in the previously ablated nodes all occurred within 11 months of the first EA and 2 were satisfactorily retreated with EA, 2 had reoperative surgery and 1 had RFA. The discovery of new NNM outside the ablated sites seen in most published studies likely represents a predictable consequence of following node-positive PTC patients with extremely sensitive Doppler flow monitoring and the increasing resolution of more recent sonographic probes [8].

An accompanying Journal of Clinical Endocrinology and Metabolism commentary [4] to the Frich paper [10] in June 2022 cautioned "How best to reduce the rates of regrowth in ablated NNM certainly requires further study, and more long-term results to compare with Frich and colleagues [10] are needed before we can establish EA as an acceptable part of recurrent APTC management." Since we had not encountered tumor regrowth in the 124 satisfactorily ablated NNM of our 83 patients treated during 1993-2000 [26] followed on average for 5 years, we felt obliged to look at a new study group of patients with APTC who (1) had EA during 2001-2017 for recurrent disease in not more than 4 NNM, (2) had previously undergone potentially curative thyroidectomy, extensive nodal resection, and postoperative RRA with negative post-RAI WBS, and (3) had been followed by sonography at our institution by our multidisciplinary team for at least 4 consecutive years.

In this present study we have demonstrated that our 71 biopsy-proven NNM after 181 ethanol injections all shrank (mean volume reduction of 93%) and nodal hypervascularity was eliminated. Moreover, 38 NNM (54%) disappeared on neck sonography. The remaining 33 NNM were identifiable as hypovascular foci with volume reductions of 45% to 97% observed (median 81%). From the standpoint of the patients with APTC, final results were considered to be ideal or near-ideal in 55% and satisfactory in 45%. In this study, where 40 patients were followed after EA from 66 to 269 months (median 14 years), we found no evidence of intranodal tumor regrowth (so-called "re-recurrence") in NNM that were satisfactorily ablated by ethanol.

The reasons why we do not see, after more than 30 years of employing EA to control nodal recurrences in APTC, evidence in this study of intranodal tumor regrowth requiring possible surgical intervention are likely multifactorial. First, with the 3 staff radiologists (J.W.C., C.C.R., and R.A.L.) selected to perform the initial ablations we likely have the most experienced team worldwide in applying this therapeutic modality to tiny NNM in patients with stage I APTC and this may also explain the absence of vocal cord dysfunction in this series of patients whose first EA was performed some 20 years after our first patient with DTC was treated with EA [8]. As stated earlier in this discussion, patients with node-positive stage I APTC have been seen daily in recent years in Mayo's Division of Endocrinology and evaluated for possible EA which is now performed several times weekly to treat these patients referred for consideration of alternatives to more neck surgery or active surveillance.

The second reason for our not observing intranodal tumor regrowth likely relates to the quality of the reporting of changes in dimensions (diameters and volume) and Doppler flow findings in each individual NNM ablated. Not only were the present nodal dimensions compared to baseline as well as last visit in the contemporary radiology report for each ablated node, but, moreover, our most experienced interventional sonographer (R.A.L.) took weeks of time in 2023 to check all the images and the calculated dimensions as well as

recalculating all volume reductions for the purpose of this study. Additionally, these 40 study patients had, as described in the details of our follow-up protocol, a median of 11 diagnostic neck sonograms reported by several very experienced consultant radiologists during their management at Mayo Clinic. Lastly, as stated in the materials and methods section, when we saw a NNM whose volume was inadequately reduced or demonstrated a tiny amount of Doppler flow, where indicated, we again treated with more ethanol on the basis that our treatment to date had been incomplete. At last follow-up we were satisfied that either an ablated NNM had truly been eliminated or it had been treated on multiple occasions and followed for enough years to show stability of shrinkage.

Clearly the attainment of excellent final results for controlling NNM with EA requires an initial learning curve, as likely evidenced by our nodal disappearance rates in our patients with stage I APTC. These rates were 31% as reported in 2002 [16], 46% in 2012 [26] and 54% in the present study. We have in our earlier reports [4, 9, 11, 16, 26] emphasized the safety of EA but do recognize that the commonest complication of EA [27, 28] has been transient hoarseness related to RLN dysfunction and likely caused by extravasation of ethanol on injection. Two recent Korean meta-analyses have quantitated the risk of this post-procedure complication as between 1.6% [27] and 2.7% [28]. We did report in 2013 1 case of temporary hoarseness [9] resulting from the injection of 0.2 mL of ethanol into a level IV NNM in the context of a 65-year-old patient's 11th documented "recurrence" and his 8th course of EA. We have, by choosing carefully our 3 experienced radiologists, avoided such a complication in this series of 40 patients receiving 181 ethanol injections. Review of contemporary real-time results from 109 patients with PTC managed by EA and reported in the past 2 years from centers in Norway [10], United States [24], and Spain [25] reveals a 2.8% rate of post-EA transient RLN dysfunction, a complication that we believe may be minimized by meticulous intranodal ethanol injection.

Last year we published a paper [29] describing the long-term efficacy of EA in controlling NNM in childhood PTC where we suggested that "in the clinical environment of 2023, the management of postoperative NNM in childhood PTC, as advised by recent guidelines, will for the foreseeable future continue to range on one end of the spectrum between those who would treat now with either reoperative surgery or further ^{131}I and on the other end those who might favor active surveillance. However, as shown in the present study, EA can effectively control postoperative NNM and the results are durable, based on the median follow-up for our ablated patients of 16 years." Such remarks we feel may now also be applied to the larger young adult population with node-positive pTNM stage I PTC. And, clearly, we eagerly await updates to be published in 2024 by the relevant ATA Committees for both the Adult [30] and Pediatric [31] DTC Management Guidelines to determine the future of MIT in managing postoperative NNM.

Based on the long-term results of the present adult and recently published childhood [29] studies we are convinced that for pTNM stage I patients with neck nodal recurrences (1) who do not wish further neck surgery, (2) are unconvinced of the efficacy of repeated radioiodine treatments, and (3) may be uncomfortable with active surveillance of biopsy-proven NNM, US-guided EA represents a very well-tolerated, safe, inexpensive, and minimally invasive outpatient management option. Although we are encouraged by the published results from American centers in Providence [22] and Minneapolis [24] and overjoyed by the use of EA in managing NNM in APTC in several other countries including Korea [27, 28, 32], Norway [10, 20], Italy [33], and Spain [24, 26], it is our hope that this novel inexpensive outpatient treatment will in the near future be made more widely available to patients with stage I PTC worldwide by physicians, whether they be radiologists, endocrinologists or any other medical practitioner possessing the special skills of safely biopsying and injecting under US guidance small cervical NNM. We earnestly hope that, after 31 years of EA for NNM in PTC practice and, with the results of this study and others like it, our physician colleagues managing low-risk PTC patients will be encouraged to make greater use of this therapeutic modality in their local centers of excellence.

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Prof. Hay has relished the challenge of looking after these 40 study patients since 2001 and gives thanks to his wife of 50 years, Prof. Eileen Hay, for encouraging him since 1991 to pursue his interest in therapeutic ethanol. Prof. Hay dedicates this paper to the memory of the late C.C.K., who 31 years ago permitted I.D.H and J.W.C. to treat her NNM with a novel alternative therapy.

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Disclosures

The authors have nothing to disclose.

Data Availability

Data sharing is not applicable to this article because no data sets were generated or analyzed during the present study.

Prior Presentation

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