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**Clinical Research Article**

# Long-term Effectiveness of Ethanol Ablation in Controlling Neck Nodal Metastases in Childhood Papillary Thyroid Cancer

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## Abstract

**Context:** Childhood papillary thyroid carcinoma (CPTC), despite bilateral thyroidectomy, nodal dissection and radioiodine remnant ablation (RRA), recurs within neck nodal metastases (NNM) in 33% within 20 postoperative years. These NNM are usually treated with reoperation or further radioiodine. Ethanol ablation (EA) may be considered when numbers of NNM are limited.

**Objective:** We studied the long-term results of EA in 14 patients presenting with CPTC during 1978 to 2013 and having EA for NNM during 2000 to 2018.

**Methods:** Cytologic diagnoses of 20 NNM (median diameter 9 mm; median volume 203 $mm^3$) were biopsy proven. EA was performed during 2 outpatient sessions under local anesthesia; total volume injected ranged from 0.1 to 2.8 cc (median 0.7). All were followed regularly by sonography and underwent volume recalculation and intranodal Doppler flow measurements. Successful ablation required reduction both in NNM volume and vascularity.

**Results:** Post EA, patients were followed for 5 to 20 years (median 16). There were no complications, including postprocedure hoarseness. All 20 NNM shrank (mean by 87%) and Doppler flow eliminated in 19 of 20. After EA, 11 NNM (55%) disappeared on sonography; 8 of 11 before 20 months. Nine ablated foci were still identifiable after a median of 147 months; only one identifiable 5-mm NNM retained flow. Median serum Tg post EA was 0.6 ng/mL. Only one patient had an increase in Tg attributed to lung metastases.

**Conclusion:** EA of NNM in CPTC is effective and safe. Our results suggest that for CPTC patients who do not wish further surgery and are uncomfortable with active surveillance of NNM, EA represents a minimally invasive outpatient management option.

**Key Words:** PTC, children, ethanol ablation, nodal metastases, outcome

**Abbreviations**: $^{131}$I, radioactive $^{131}$iodine; APTC, adult papillary thyroid carcinoma; AS, active surveillance; ATA, American Thyroid Association; CPTC, childhood papillary thyroid carcinoma; DTC, differentiated thyroid carcinoma; EA, ethanol ablation; $LT_4$, levothyroxine; MIT, minimal invasive therapies; NNM, neck nodal metastases; PET, positron emission tomography; PTC, papillary thyroid carcinoma; RFA, radiofrequency ablation; RRA, radioiodine remnant ablation; US, ultrasound; Tg, thyroglobulin; TSH, thyrotropin; TT, total thyroidectomy.

The incidence of thyroid cancer in children and adolescents, a condition that was globally very rare until around the year 2000 [1], has increased rapidly since the early 1990s in many countries [2]. Cause-specific mortality rates, however, have remained extremely low at fewer than 0.1 deaths per million person-years, corresponding to fewer than 10 deaths per year [3] in most countries. Among 15- to 19-year-old adolescents, thyroid cancer is the eighth most frequently diagnosed malignancy and the second most common cancer among girls [4]. Papillary thyroid carcinoma (PTC) accounts for more than 90% of all childhood cases [4] and increasing recognition or overdiagnosis of childhood PTC (CPTC) may result in "overtreatment, lifelong medical care, and side effects that can affect quality of life" [3].

Despite potentially curative bilateral thyroidectomy, nodal resection, and radioiodine remnant ablation (RRA), persistent or recurrent PTC within neck nodal metastases (NNM) may be discovered in a third of CPTC patients (aged <19 years) within 20 postoperative years. Fig. 1 illustrates the 20-year occurrence rate of 33% seen in CPTC, a rate that is more than twice those rates seen for all other age groups. Typically, these persistent or recurrent NNM are treated by further

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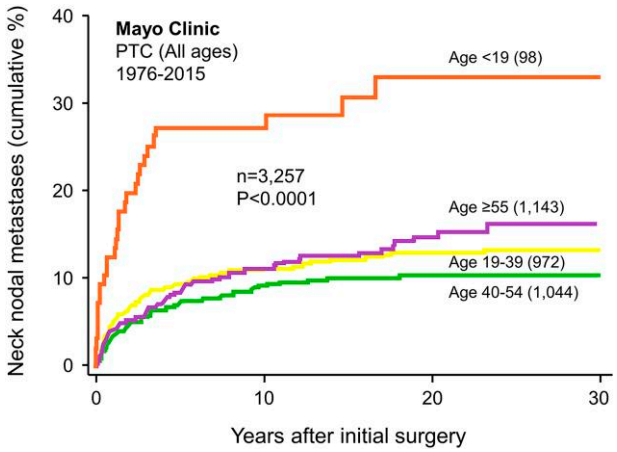


**Figure 1.** Cumulative occurrence rates of neck nodal metastases through 30 postoperative years in 3257 patients with papillary thyroid carcinoma in the NOW cohort [5] having potentially curative primary surgery at the Mayo Clinic, Rochester, Minnesota, during 1976 through 2015. The 20-year rates for patients younger than 19, aged 19 to 39, 40 to 54, and 55 years or older were 33%, 13%, 10%, and 15%, respectively. PTC, papillary thyroid carcinoma.

radioiodine treatments or secondary neck exploratory surgeries. Such procedures, unfortunately, are often associated with increased risk of recurrent laryngeal nerve or parathyroid gland injury [4].

In 2021 the European Thyroid Association clinical practice guidelines [6] recommended minimally invasive therapies (MITs) as an alternative option to surgical neck dissection 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 [7] concluded that "encouraging results suggest that minimally invasive techniques can also be used in small-size primary and locally recurrent thyroid cancer." Further support for MIT has come from Bauer [8], who advised that ultrasound (US)-guided percutaneous ethanol or radiofrequency ablation (RFA) may be considered in CPTC as appropriate "nonsurgical options with a limited number of neck metastases (1 or 2 lymph nodes), depending on the location and size of the lymph nodes."

At our institution we instituted ethanol ablation (EA) for the control of NNM in differentiated thyroid cancer in 1991 [9] and by 2023 we have employed EA at the Mayo Clinic in adult PTC (APTC) for more than 3 decades [10]. We and others [11–13] have demonstrated the long-term efficacy of this MIT in APTC, and, moreover, in 2020 we demonstrated that in a single APTC patient the technique can be repeated on at least 8 occasions to eliminate neck nodal disease [14]. In this present report, we describe for the first time the successful application of EA to the challenging problem of controlling NNM which, despite potentially curative initial management, occur frequently in adolescent and adult patients who had presented with CPTC.

## Materials and Methods

### Institutional Review Board Approval of Study

The study of ablated patients was approved by the Mayo Clinic Institutional Review Board, and all patients gave permission for their data to be included in the study.

### Initial Management of Childhood Papillary Thyroid Carcinoma in Patients Selected for Ethanol Ablation of Neck Nodal Metastases

The 14 CPTC patients (12 female and 2 male) included in this study had potentially curative primary surgery during 1978 to 2013. Their ages at presentation ranged from 12 to 18 years (median 16 years). The cases were given numbers based on the date of first EA; thus, case1 had been treated in December 2000 and case 14 in March 2018. Six of the initial surgeries were performed at the Mayo Clinic in Rochester by 2 endocrine surgeons dedicated to the CPTC practice. Six patients had primary surgeries elsewhere in the United States (4 in the North Central Midwest; 1 each in New York and Alabama). The other 2 had initial surgeries in Canada and South Africa. Eleven (86%) had an initial total thyroidectomy (TT), 2 had a unilateral lobectomy, and 1 had a near-total thyroidectomy. All 14 primary surgeries were performed with curative intent. Two (18%) of the 11 patients who had an initial TT postoperatively developed permanent hypoparathyroidism and one (9%) of the TT patients had permanent unilateral vocal cord paresis. At first surgery, all 14 patients had dissection of regional neck nodes and at surgical pathology NNM were verified. When primary surgery was performed at Mayo, a median of 12 NNM (range, 3-35) were identified when 5 to 80 (median of 25) nodes were removed and meticulously examined by surgical pathologists.

After a TT performed in 1996, one patient (case 3) had no postoperative neck radioactive $^{131}$iodine ($^{131}$I) uptake and was therefore not given radioiodine. Another (case 8), treated by TT in 2006, was advised not to have radioiodine after discussion between the treating physician (I.D.H.) and the parents of the 16-year old patient. The cumulative radioiodine doses given to the other 12 patients is illustrated in Fig. 2. Eleven patients (92%) after potentially curative surgery underwent postoperative RRA with initial $^{131}$I doses ranging from 30 to 211 mCi (median dose 50 mCi); one patient (case 4) was found at Mayo to have intrathoracic uptake on postoperative whole-body scanning and was given in 2003 an initial therapeutic dose of 100 mCi. After their initial radioiodine doses, 6 of the 12 (50%) had further doses of radioiodine; 4 having a second dose, and 2 having a second and a third dose. As illustrated in Fig. 2, 8 (67%) had cumulative doses of 30 to 169 mCi (median 117 mCi), while 4 (33%) had doses of 300 mCi or more (range, 300-390 mCi) with a median dose of 332 mCi. Despite this initial, somewhat aggressive, management with potentially curative surgery and in 86% postoperative radioiodine treatments, 9 patients (64%), prior to being considered for EA, had undergone further neck reexplorations (total of 17 neck dissections; range 1-4, median of 2) for persistent/recurrent disease in NNM. The patients with cases 5 and 9, who initially underwent potentially curative lobectomies, had completion thyroidectomies at the time of their first of 4 neck reexplorations and subsequently received cumulative radioiodine doses of 90 mCi and 390 mCi, respectively.

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

The 6 CPTC patients who had initial surgery during 1978 through 2013 at Mayo ranged in age at disease presentation from 12 to 17 years (median 16) and were initially cared for by Mayo staff pediatric endocrinologists. When being evaluated during 2003 to 2018 for possible EA of NNM, 3 were

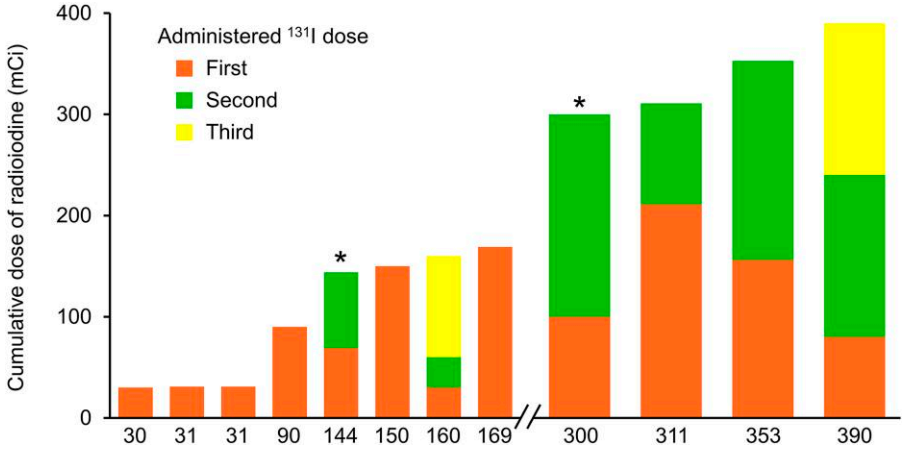


**Figure 2.** Cumulative doses of therapeutic radioiodine administered to those 12 childhood papillary thyroid carcinoma patients who received such postoperative treatment during definitive management of their primary diseases. The exact doses are given on the horizontal axis (30-390 mCi). The asterisks above the 5th and 9th columns denote the 2 patients (cases 10 and 4) who were given radioiodine in response to the discovery of pulmonary nodules suspected to be metastatic.

still considered children (age < 19), and the others (patient cases 3, 6, and 8), who had graduated to care by an adult endocrinologist, were aged 19, 23, and 44 years. These 6 patients operated on at Mayo were followed for a median of 13 years at Mayo Rochester, and during that period they had a median of 11 diagnostic neck USs and 9 care episodes supervised by the principal investigator (PI) (I.D.H.). Of the 8 patients referred to Mayo during 2000 to 2013 for postoperative evaluation directed at identifying recurrent disease, only 1 (patient case 12) was yet in pediatric care; the other 7 (patient cases 1, 2, 5, 7, 9, 11, and 13), as well as patient cases 3, 6, and 8, were now being cared for by one adult thyroidologist, the PI. These 8 patients operated on elsewhere were followed for a median of 16 years in Rochester and during that time had a median of 15 diagnostic neck USs and 12 care episodes supervised by the PI. The time interval from initial surgery to consideration of EA of NNM was variable, ranging from as early as 15 postoperative months to as late as 31 years (median 7 years). Six patients (or 43%) had their recurrences within 3 years of primary surgery and were considered to have early recurrences. The later recurrences (≥ 4 years) were divided equally between those 4 occurring between 4 and 19 years, and the final 4 occurring during 20 to 31 years after primary surgery.

In the course of their Mayo evaluations during 2000 through 2018, the 14 patients were found to have a total of 20 NNM that were confirmed to be metastatic PTC by examination of cytological specimens obtained by US-guided biopsy. Nine patients had a single NNM; 4 had 2, and the first patient (case 1), evaluated and ablated in 2000, was the only CPTC patient in our series who had 3 NNM selected for EA. All 14 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 and their families regarding the available options to manage the identified and biopsy-proven PTC in NNM. When the 14 patients elected to undergo management with EA, their clinical details were entered prospectively into an institutional review board–approved computerized registry of more than 200 patients with differentiated thyroid cancer whose care had been supervised by the PI since 1991.

## Details of the Ethanol Ablation Procedure

All EA procedures for NNM in CPTC during 2000 to 2018 were performed by 3 staff radiologists (R.A.L., C.C.R., and J.W.C.) who by 2000 had a collective experience of more than 50 years at Mayo Clinic in sonography and US-guided interventions. The sonography scanner and the transducers used were as previously described [14, 15]. Each NNM was carefully measured and the pretreatment volume (in millimeters cubed, $mm^3$) calculated using the ellipsoid formula [16] of anteroposterior X transverse X longitudinal diameters X 0.52. Color Doppler ultrasonography was performed to document the 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 [17] and as reported initially for NNM elimination by Lewis and colleagues in 2002 [18]. The CPTC patients 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 decided at the time of each ablative session. The treating radiologist obtained signed informed consent from the 14 CPTC patients or, where applicable, their parents, before initiating the course of treatment.

## Follow-up Protocol

Routinely, the CPTC 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 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 to 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. 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 6 (43%) of the 14 patients were still being followed at Mayo, the other 8 (57%), at a median of 18 years post EA, were being followed by local physicians. For this study the medical records from Mayo Clinic, as well as those of the local physicians, were reviewed in March 2023 and, when indicated, follow-up obtained directly from the patients themselves. At last follow-up the 14 patients had been followed since EA for a median of 16 years (range, 5-20 years).

## Results

### Dimensions and Anatomical Locations of 20 Neck Nodal Metastases Selected for Ethanol Ablation

The maximum diameters of the 20 NNM chosen for EA ranged from 5 to 16 mm, and 11 (55%) had nodal diameters less than 1 cm. The median diameter of the biopsy-proven NNM was 9 mm. Volumes of the NNM ranged from 9 to 1198 $mm^3$ with a median value of 203 $mm^3$. Eleven (55%) had a volume of less than 300 $mm^3$. Twelve (60%) of the NNM were situated in the central compartment (10 at level VI; 2 at level VII); the other 8 (40%) were in the lateral neck (2 at level II, 1 at level III, and 5 at level IV).

### Details of Ethanol Ablation Treatment Sessions

The 20 selected NNM were treated with a total of 49 ethanol injections. During 2000 to 2004, 5 NNM (in patient cases 1, 3, and 6) were treated with single injections ranging in volume from 0.1 to 0.4 cc (median 0.15 cc). From 2005, as the radiologists became more comfortable with treating NNM with larger volumes, it became routine for NNM to be treated on consecutive days in 2 sessions. Nine nodes were considered to be adequately treated with 2 such 2-day sessions only, and total ethanol volume injected ranged from 0.6 to 1.4 cc (median 0.65 cc). Two other nodes found in patient cases 2 and 13 (with pre-EA volumes of 757 and 166 $mm^3$) had the initial 2-day sessions but required a third injection at 3 to 6 months (for total volumes of 1.35 and 0.9 cc) to completely eliminate intranodal blood flow. In patient case 5, 1 large lateral node of 1198 $mm^3$ ($9 \times 16 \times 16$ mm) was initially treated in a 2-day session with 1.1 cc and then again treated at 3 months for 3 consecutive days with a further 0.7 cc, for a total of 1.8 cc to permit elimination of flow. In that same patient a smaller midline level VII NNM of 309 $mm^3$ was also identified, and this was treated over 3 days with a total of 0.6 cc to enable cessation of flow.

Patient case 8 (operated on at Mayo in 2003 and ablated in 2006) required a total of 9 ethanol injections to control her 2 relatively small NNM situated at levels 4 and 6 with pre-EA volumes of 104 and 166 $mm^3$. In a 2-day session in February 2006, she had 0.4 mL injected into the level VI NNM and 0.9 cc into the level IV node. Because of persistent intranodal vascularity, she had in June 2006 a further 2-day treatment session during which she had 0.8 cc injected into the level VI NNM (total volume 1.2 cc) and 1.9 cc into the level IV NNM (total volume 2.8 cc). From October 2007 through January 2020 the treated level VI NNM was identifiable on 11 neck sonograms but was stable in size at $4 \times 4 \times 5$ mm (volume 42 $mm^3$) with minimal intranodal vascularity and serum thyroglobulin (Tg) levels on thyrotropin (TSH)-suppressive levothyroxine ($LT_4$) therapy ranging between 0.3 and 0.5 ng/mL. The minor vascularity seen on Doppler was more obvious when a decision was made by a treating nurse practitioner to reduce the patient's TSH-suppressive $LT_4$ dose from 0.137 mg daily to 0.1 mg and the patient's serum TSH rose from 0.01 to 0.8 mIU/L and Tg from 0.4 to 1.1 ng/mL, at which point her then supervising staff endocrinologist elected to treat this node in March 2022 with a fifth ethanol dose of 0.1 cc for a cumulative ethanol volume over 16 years of 1.3 cc.

### Long-term Efficacy of Ethanol Ablation in Local Control of 20 Neck Nodal Metastases in 14 Childhood Papillary Thyroid Carcinoma Patients

Successful ablation required reduction in nodal volume and reduction of intranodal vascularity by Doppler flow measurement. An ideal result would therefore be the complete disappearance of the ablated NNM. In this study all 20 ablated nodes had reduction in volume with an average shrinkage of 87%, and the majority (55%) disappeared after a median of 19 months. Follow-up in the 14 CPTC patients when measured from the date of initial ablation to last medical contact ranged from 5 to 20 years with a median of 16 years. No satisfactorily ablated NNM grew after EA during the follow-up period. Only one NNM (5%), as described earlier in the description of patient case 8, retained minimal vascularity despite 5 injections administered over 16 years. Thus, 100% of the 20 ablated NNM experienced nodal volume reduction and 95% had complete elimination of intranodal vascularity.

### Postethanol Ablation Disappearance of 11 Neck Nodal Metastases in 8 Childhood Papillary Thyroid Carcinoma Patients

During follow-up 11 of 20 ablated NNM (55%) disappeared on neck sonography. Pre ablation the NNM volumes had ranged between 9 and 491 $mm^3$ (median 206 $mm^3$). Eight of 11 (73%) NNM were early recurrences and had been diagnosed within 3 years of initial surgery. Fig. 3 demonstrates the timing from ablation to disappearance, which ranged

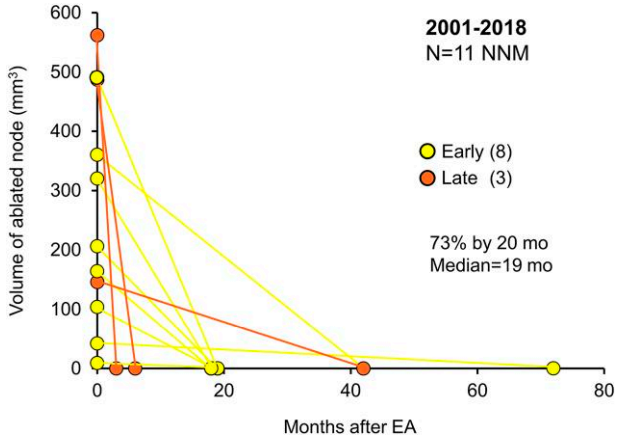


**Figure 3.** Timing of disappearance of 11 neck nodal metastases arranged by preablation volume (vertical axis) and number of months after ablation to disappearance (horizontal axis). A total of 73% of these metastases disappeared by 20 months after ablation; the median time for disappearance was 19 months. EA, ethanol ablation; NNM, neck nodal metastases.

from 3 months to 6 years and averaged 19 postablation months.

### Shrinkage of 9 Ablated Neck Nodal Metastases Still Identifiable on Sonography

At latest follow-up 9 NNM (8 avascular) with a median shrinkage of 76% were still identifiable on sonography. Fig. 4 compares the mean shrinkage in those 5 identifiable NNM that had a pre-EA volume of less than 300 $mm^3$ with those 4 with a pre-EA volume of 300 $mm^3$ or more. With volumes of less than 300 $mm^3$, the mean shrinkage was 76%; for those with volumes of 300 $mm^3$, shrinkage was similar at 75%. Fig. 5 illustrates the range of shrinkage (12%-93%) in the 9 still identifiable NNM; the median shrinkage was 76%. The only identifiable NNM that had minimal vascularity despite 5 ethanol injections showed a 53% shrinkage and was followed for 193 months after initial EA. The horizontal axis shows the number of months since EA at last follow-up, which ranged from 99 to 170 months with a median of 12.3 years (147 months).

### Changes in Serum Thyroglobulin (Tg) After Ethanol Ablation in 12 Childhood Papillary Thyroid Carcinoma Patients Without Tg Autoantibodies

Prior to first EA serum Tg levels measured, with the patients on TSH-suppressive $LT_4$ therapy, from 0.8 to 18 ng/mL, with a median of 4.2 ng/mL. Fig. 6 illustrates the changes occurring in serum Tg between first EA and latest follow-up visit. The Tg levels at last Mayo follow-up were lower in all but one patient (case 10), whose serum Tg rose from 1 to 2.2 ng/mL; this rise in Tg was associated with the development of lung micronodules on computed tomography of the chest. The median serum Tg after EA for the 12 patients was 0.6 ng/mL; in these patients when serum Tg was less than 2 ng/mL, there was no demonstrable evidence of active disease on the latest high-resolution sonograms. Although after EA 4 patients subsequently required further radioactive iodine or compartmental dissection for previously untreated metastatic disease, the observed Tg changes in the majority (71%) of patients likely reflected the efficacy of the EA, which had been the last cytoreductive treatment for these 14 NNM.

### Early or Late Complications of the Ethanol Ablation Procedures

Other than minor neck discomfort typically lasting from 6 to 12 hours after EA, there were no other complications attributable to any of the 49 ethanol injections administered by our very experienced staff radiologists. Despite 60% of the ablated NNM being situated within the central compartment of the neck, no example of postprocedure hoarseness was observed in this series.

### Progression of Disease in Other Anatomic Sites During Follow-up

During post-EA follow-up, 3 CPTC patients had later novel recurrences in NNM and a decision was made to reoperate primarily on the basis of the location and extent of nodal disease. The first of these was patient case 2 who had in 2002 successful ablation of a 757-$mm^3$ level VI NNM but in 2006 had extensive new biopsy-proven NNM in the bilateral lower neck necessitating a bilateral central nodal dissection that yielded 7 NNM from bilateral level VI. The second example was the problematic patient case 8 whose level IV and level VI NNM had been treated with a total of 4 injections in February and June 2006. In October 2007 the level IV NNM of 104 $mm^3$ had disappeared but a new suspicious 17-mm node was found in the mid left jugular chain and was found to have positive cytology on guided biopsy. A decision was made to perform a left selective dissection involving levels III, IV, and anterior V. Thirteen nodes were removed and 6 proved to be NNM. Unfortunately, the 42-$mm^3$ level VI node was not excised and persisted.

The final example of progression in other neck nodes was patient case 10, whose 364-$mm^3$ level II NNM was successfully ablated in 2010 but in 2013 a positive biopsy of a 17-mm NNM led to a selective unilateral dissection of levels II and III yielding 2 NNM from 8 nodes removed. Careful examination by surgical pathology did not find evidence in these 3 reoperated cases of the ablated NNM that had been satisfactorily treated.

Intrathoracic spread was observed in 2 patients (cases 4 and 10); both were managed by $^{131}I$ therapy. Complete response was observed in patient case 4 and stabilization in patient case 10.

## Discussion

In 2015 the American Thyroid Association (ATA) Guidelines for Pediatric Thyroid Nodules and Cancer [4] stated in their Recommendation 28(A) that "the decision to treat or to observe structurally identifiable cervical disease should be individualized and include considerations of age, initial ATA Pediatric Risk classification, the presence of distant metastases, and prior treatment history." In 2022 a UK National Clinical Practice Consensus Guideline [19] recommended that, if persistent local structural disease is detected on a postoperative neck sonogram, further surgical resection should be considered in a multidisciplinary team discussion [19]. After further surgical resection they advised consideration of therapeutic radioiodine, especially if there was imaging or biochemical evidence of residual disease not amenable to surgery.

Dr Andrew Bauer, one of the lead authors of the 2015 ATA management guidelines, noted in a 2020 review [20] that EA or RFA may be considered as a possible treatment option in patients with a limited number of NNM and dependent on the location and size of the nodes. More recently, an international expert panel from 9 international specialist societies, led by the American Head and Neck Society [12], approved either RFA or EA as a "suitable first-line therapy" for NNM in adult PTC patients. To date, there has been only one published report describing the use of RFA in controlling NNM in patients presenting with CPTC [21]. In this study 10 NNM in 5 children and adolescents were treated with RFA and followed for a mean time of 4.3 years. All nodes decreased in size and 9 (90%) NNM completely disappeared. There were no procedure-related complications such as hematoma or nerve injury. The authors [21] concluded that "RFA may provide another alternative to the existing therapeutic modalities for cervical metastatic lymph nodes in children and adolescents with PTC."

Our group at Mayo first used EA to successfully ablate 3 NNM in a 15-year-old girl with CPTC during 2000 to 2001. By 2013 we had ablated a further 4 children and had followed them on average for 7.3 years by the time we

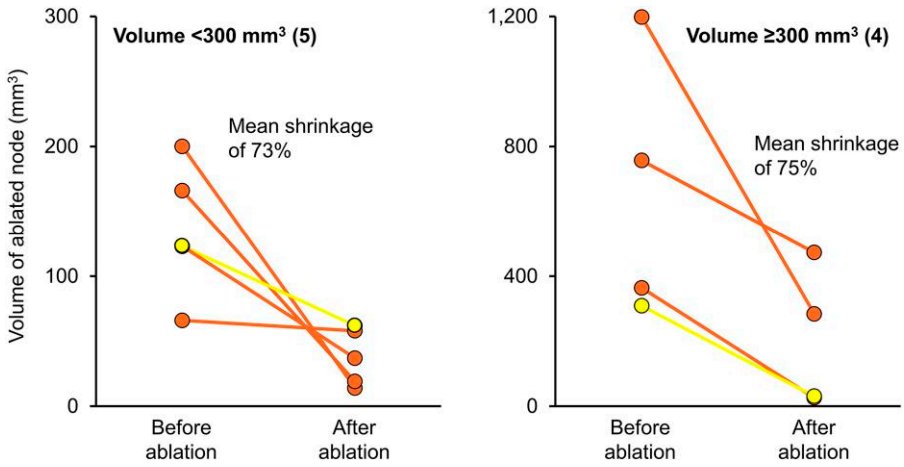


**Figure 4.** Decreases in volume observed after ethanol ablation in 9 still identifiable neck nodal metastases. Figures in left panel refer to those 5 nodes (volume range, 66-200 $mm^3$) that were less than 300 $mm^3$ before ablation; figures in right panel refer to those 4 nodes (volume range, 309-1198 $mm^3$) that were 300 $mm^3$ or more before ablation. Seven (78%) of the still identifiable nodes were considered later recurrences (>3 postablation years).

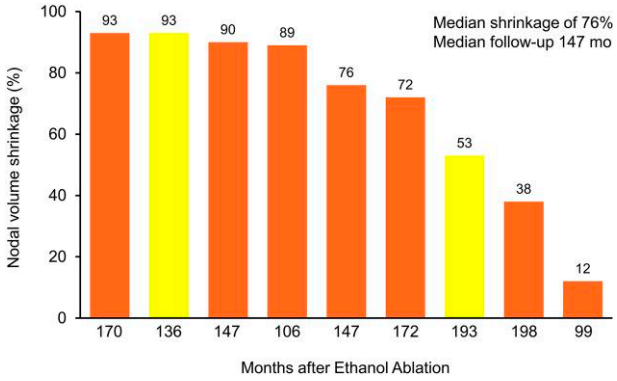


**Figure 5.** Nodal volume shrinkage (range, 12%-83%; median 76%) after ethanol ablation in 9 still identifiable neck nodal metastases (NNM). The number above each column represents the actual nodal volume shrinkage (%) observed in an individual ablated NNM. The numbers on the horizontal axis denote the numbers of follow-up months for each ablated NNM.

reported our preliminary results in 2014 to the ATA [22]. We had treated 8 NNM (mean diameter 8 mm) with EA delivered by 11 injections; all NNM decreased in size and 6 (75%) completely disappeared. There were no complications and none of the ablated nodes required further intervention. Our 2014 conclusion [22] was that "EA for selected persistent/recurrent NNM in adolescents with PTC has proved both safe and effective. Moreover, it is also considerably cheaper and less dangerous than the alternatives of re-exploratory surgery or further treatment with higher radioiodine doses." Clearly such preliminary studies have limitations in part due to the rarity of CPTC patients and future prospective studies would certainly be enhanced by the inclusion of a comparator group, whether managed by active surveillance (AS) or by selective compartmental neck dissection. To date, no such study, to our knowledge, yet exists in the pediatric PTC literature.

In 2012 Robenshtok et al [23] reported on "the first study to describe the natural history of suspicious cervical lymph nodes identified after initial therapy for PTC and followed with serial US examinations for several years." In the decade following that publication, reports of an AS approach to small NNM in PTC have been scarce and, to our knowledge, none exist in the pediatric endocrinological literature. In recent months an Argentinian group reported a study [24] of 50 PTC patients (age range 18-75 years; median age 41 years) who had suspicious neck nodes with cytologic confirmation of metastatic disease and were followed without intervention for a median of 29 months (range, 12-144 months). Despite 22% requiring surgery or $^{131}I$ therapy, the authors concluded [24] that AS of small NNM in APTC could be a feasible alternative to immediate surgery in "properly selected patients."

In November 2022, Ho and his multidisciplinary colleagues [25] observed that in the clinical arena of managing small-volume PTC, "other interventions that straddle surgery and surveillance, such as radiofrequency ablation, are also emerging, though are not without flaws." As we at Mayo look back at more than 30 years of performing US-guided interventions "straddling surgery and surveillance" we recognize that, in our attempt to control NNM in patients presenting with CPTC during 2000 to 2018, we treated with EA 14 individuals who were not at risk of cause-specific mortality Even those 2, who had evidence of distant spread to the lungs, lived with their disease and are likely not destined to die of their PTC. In pursing local control or even "cure" in the management of NNM in CPTC, we were mindful of the Hippocratic credo of "semper primum non nocere" as well as a longstanding belief in the principles of Blake Cady [26] that in the management of PTC one should always strive "to let the punishment fit the crime." Thus, in our experience, EA represents an alternative therapy to control NNM that can combat not only locally extensive and potentially threatening disease in APTC [9, 11] but can also be directed at the clinically indolent lesions seen in NNM, such as those we have treated in patients presenting with CPTC.

Clearly, in the clinical environment of 2023, the management of postoperative NNM in CPTC, as advised by recent guidelines [4, 19, 20], 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 AS. 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 14 ablated patients of 16 years. From our results we are convinced that, when a CPTC patient is

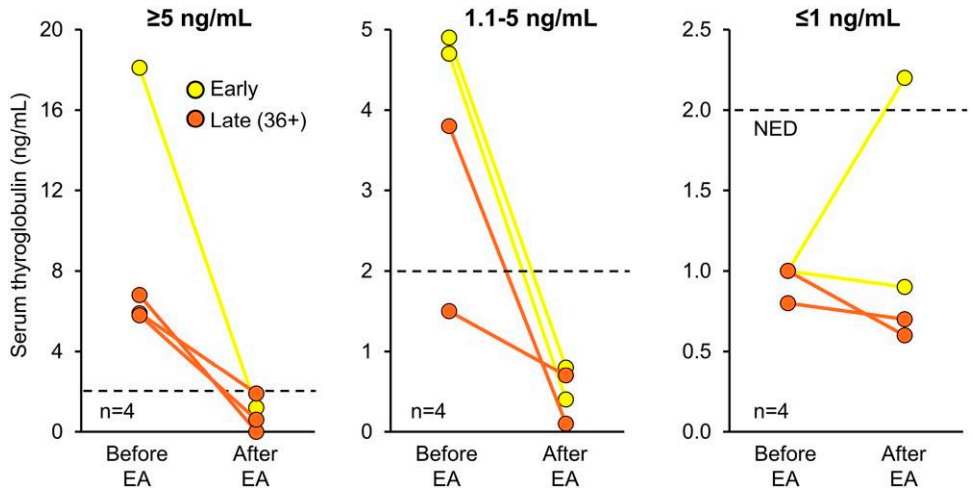


**Figure 6.** Changes in serum thyroglobulin (Tg) levels after ablation of recurrent neck nodal metastases in 12 patients presenting with childhood papillary thyroid carcinoma whose serum samples contained no interfering Tg autoantibodies. The figures in the left panel refer to those whose preablation Tg values were 5 ng/mL or higher; those in the middle panel are from patients whose initial Tg values ranged between 1 and 1.5 ng/mL; the right panel displays those with values of 1 ng/mL or less. The broken line in each panel denotes 2 ng/mL and below this value, as found in serum samples drawn at latest follow-up visits, no evidence of disease was discoverable in the latest neck sonograms. The rise in serum Tg from 1.0 to 2.2 ng/mL was found in patient 10, who had pulmonary nodules found in computed tomograms of her chest. EA, ethanol ablation.

faced with deciding on a treatment preference for biopsy-proven NNM, he or she would often rather choose a minimally invasive treatment. Moreover, we are now confident that, for CPTC patients with postoperative biopsy-proven NNM who do not wish further surgery, are unconvinced of the efficacy of repeated radioiodine treatments, and are uncomfortable with long-term AS, the option of treatment with EA represents a well-tolerated, safe, inexpensive, and minimally invasive novel outpatient management option.

Commenting in 2012 on "deceptively simple options" in the management of recurrent/persistent NNM in PTC, Burman [27] recommended that "percutaneous ethanol injection has been shown to be effective and should be used more frequently as it is a simple, effective outpatient procedure." More recently, as our Mayo colleagues [28] in Florida have stated, "in properly selected patients with nodal metastases from PTC, compared with other locoregional therapy options, ethanol ablation has the greatest potential for applicability anywhere in the world," and now we are convinced that this can also apply to patients who develop PTC during childhood.

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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.

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