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Elimination of Locoregional Recurrences and Skin Metastases in Papillary Thyroid Cancer by Ethanol Ablation and Mohs Surgery

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Ultrasound-guided percutaneous ethanol ablation procedures for locoregional recurrences in papillary thyroid carcinoma (PTC) can be repeatedly performed over years. Skin metastases (SM) from PTC generally portend a lethal prognosis. Our patient case report demonstrates the innovative use in low-risk PTC (LRPTC) of treatment modalities designed to prevent neck re-explorations and capable of eliminating both locoregional recurrences and SM. In 2004, a 48-year-old man presented with neck nodal metastases due to PTC. He underwent a near-total thyroidectomy and nodal dissection, confirming an 8-mm PTC involving 2 ipsilateral node metastases. Postoperatively, he received 2 doses of radioactive iodine (RAI) for remnant uptake (cumulative dose 338 mCi); posttherapy scanning was unrevealing. In 2007, he underwent right neck dissection for further node metastases. In 2008, a guided biopsy confirmed a level IV node metastasis. He was referred to our institution for ethanol ablation. Two node metastases were ablated and subsequently disappeared. During 2010-2016, he developed an additional 6 node metastases, which were treated with ethanol ablation; all disappeared on high-resolution sonography. FDG-PET-CT scans in 2009 and 2016 were negative for distant spread. In 2016, a SM in his right neck was removed by dermatologic surgery. In 2017-2018, 2 further SM were excised with negative margins, one after Mohs surgery. He has now been disease-free for 20 months. In conclusion, despite 3 neck surgeries and 2 RAI therapies, our patient repeatedly developed both locoregional recurrences and SM. All 11 disease foci were eliminated with minimally invasive procedures which should more often be considered as effective treatment options in LRPTC.

Key Words: ethanol injection, PTC, skin metastasis, locoregional recurrence, dermatologic surgery, long-term prognosis

Low-risk papillary thyroid cancer (LRPTC), the commonest endocrine malignancy seen globally in 2020, is presently being overdiagnosed and likely often overtreated [1-7]. Such patients typically enjoy a >99% cause-specific survival, as predicted by either a MACIS score [8] of <6 or an AJCC pTNM (8th edition) stage of I. A recently published long-term follow-up study showed that only 0.7% of 2688 LRPTC (MACIS scores <6) adult patients, who

Abbreviations: ATA, American Thyroid Association;CT, computed tomography;DTC, differentiated thyroid cancer; FDG, fluorodeoxyglucose; LRPTC, low-risk papillary thyroid cancer;PET, positron emission tomography; PTC, papillary thyroid cancer;PTM, papillary thyroid microcarcinoma;RAI, radioactive iodine;SM, skin metastases;Tg, thyroglobulin;TSH, thyrotropin (thyroid stimulating hormone);US, ultrasound;USGB, ultrasound-guided biopsy.

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were definitively treated at Mayo Clinic during 1976-2015, experienced death from papillary thyroid cancer (PTC) by 30 postoperative years [9].

Despite surgery and radioiodine remnant ablation, tumors in LRPTC can recur, but fortunately >90% of such events are in the neck and the vast majority occur in regional neck nodes [9]. Ultrasound-guided percutaneous ethanol ablation for locoregional recurrences in PTC was first introduced to clinical practice in 1993 [10]. It is not appreciated that such noninvasive ablations can often be repeated in an individual patient over many years [11].

Skin metastases (SM) from thyroid carcinoma are extremely rare [12], with a reported frequency of 0.8% in all PTC patients [12] and from 1% to 7% in those with distant spread [13, 14]. A recent systematic review [15] sought to characterize "rare metastatic sites" in differentiated thyroid cancer; when excluding lung, bone, and lymph nodal involvement, the brain (44%) was the most common rare metastatic site, followed by the skin (17%) and the liver (8%). In a 5-decade study of 100 cases of PTC [13] from the Mayo Clinic, the second anatomic site for distant spread was brain in 34%, while skin and liver metastases each accounted for 3%.

It is extremely unusual for SM to be associated with a papillary thyroid microcarcinoma (PTM) and we have only been able to identify one such case [16] where a solitary scalp metastasis was the initial manifestation of what was said to be a PTM of 5 mm in diameter. Of 1376 cases of adult PTM from Mayo managed during 1936-2015, we have only found (after an average follow-up of 15.2 years), 7 patients with distant metastases (0.5%) and none involved the skin [9]. SM in PTC most often occur in the setting of tumors with high-risk features [17-21] and some have exhibited somatic genomic alterations including the *BRAFV600E* mutation [19, 21] and aberrations involving the *RET* proto-oncogene [17]. Typically, SM in PTC occur in the setting of widespread disseminated disease [18-20] with a reported average survival of only 19 months after SM diagnosis.

In this report, we present a unique case of an adult PTM patient with multiple postoperative "recurrences" that we believe can provide insights into novel and minimally invasive strategies for the elimination of locoregional recurrences and SM in LRPTC.

Illustrative Case

Initial management (2004-2008)

A 48-year old man presented in 2004 with a 3-cm right neck mass. Open biopsy revealed a neck node metastasis due to PTC. He had a near-total thyroidectomy and right neck nodal dissection for a right lobar 8-mm PTC involving 2 ipsilateral node metastases (pT1aN1b). His postoperative iodine-131 (^{131}I) uptake at 24 hours was 4%, localized to the central neck; he was given 150 mCi of radioactive iodine (RAI). Seven months later, he had a neck uptake of 0.4% and was given a further 188 mCi of RAI. Posttherapy whole-body scanning revealed no evidence of distant spread. Despite this aggressive initial management, during 2005-2006 the patient had increasing serum thyroglobulin (Tg) levels while on thyrotropin (thyroid stimulating hormone; TSH) suppression therapy. In 2006, a fluorodeoxyglucose (FDG) positron emission tomography– computed tomography (PET-CT) scan was negative and a rhTSH-stimulated body scan was unrevealing. In 2007, he had a negative neck CT scan, but a neck ultrasound (US) was suspicious for persistent node metastases in the right neck, leading to a third surgery (multi-compartmental dissection of right neck) and the removal of multiple node metastases. The initial postoperative serum Tg was 2 ng/mL, but by 2008, the level had risen and an US-guided biopsy (USGB) confirmed a right level IV node metastasis. The patient was opposed to having a fourth neck surgery and was referred by his local endocrinologist for consideration of ethanol ablation.

Multiple locoregional recurrences managed by ethanol ablation (2008-2015)

Sonography at Mayo Clinic revealed 2 suspicious node metastases in the right neck (numbered 1 and 2 in Table 1). A previously unidentified hypervascular node of 7-mm diameter

Table 1. Details of 8 Ablated Node Metastases, Ethanol Injections, and Time to Disappearance

No.	Right Neck Level	Tumor Size, mm (AP × W × L)	Volume, mm^3	Date of UPEA	Number of Injections and Therapy Sessions	Total Volume (cc)	Date of Disappearance	Time from UPEA to Disappearance (months)
1	II	6 × 5 × 7	109	08/2008	2 (1)	1.0	01/2009	5
2	IV	6 × 9 × 11	309	08/2008	4 (3)[a]	1.85	09/2010	25
3	II	6 × 6 × 9	168	12/2012	2 (1)	0.7	01/2016	37
4	V	4 × 5 × 6	62	12/2012	4 (2)[a]	1.5	12/2017	60
5	V	4 × 6 × 6	75	12/2012	2 (1)	0.8	09/2013	10
6	IV	4 × 5 × 7	73	02/2017	2 (1)	0.7	06/2017	4
7	IV	4 × 6 × 8	100	02/2017	2 (1)	0.7	12/2017	10
8	IV	4 × 4 × 5	42	02/2017	1 (1)	0.4	06/2017	4

Abbreviations: AP, anteroposterior; L, length; W, width; UPEA, ultrasound-guided percutaneous ethanol ablation.
[a]Nodules #2 and #4 required repeat injections during 2009-2017.

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(#1) was found at level II; a USGB confirmed PTC. The known node metastasis (#2) was 6 × 9 ×11 mm and implanted in the posterolateral margin of the right sternocleidomastoid muscle. Both node metastases were treated on 2 consecutive days, as previously described [10, 11]; injection details are given in Table 1. A serum Tg in August 2008 was 4.8 ng/mL while on TSH suppression. By February 2009, his serum Tg was 2.9 ng/mL (Fig. 1) and the level II node metastasis (#1) was unidentifiable (Fig. 2). The tumor volume in the larger node (#2) had dramatically fallen from 309 to 55 mm^3 (Fig. 3) but minimal Doppler flow persisted; a decision was made to re-treat with 0.65 cc of ethanol. By June 2009, the serum Tg was 2.6 ng/mL and an FDG PET-CT scan was negative for suspicious disease. Node metastasis #2 was visible but, fortunately, it had shrunk in volume by 90% to 31 mm^3 without significant Doppler flow. In March 2010, the patient had a Tg of 4.5 ng/mL and sonography revealed that node metastasis #2 was more prominent, had more Doppler flow, and had increased in volume to 73 mm^3. A further ablative injection was administered (Fig. 3). In June 2010, the Tg was 5.5 ng/mL, and neither ablated node metastasis could be identified. In September 2011, serum Tg rose further but US revealed "no evidence of recurrent PTC". The patient returned in December 2012, by which time the Tg had risen to 42 ng/mL. Neck US revealed 3 new suspicious nodes in levels II and V of the right neck. USGB confirmed PTC and node metastases #3, #4, and #5 were injected as per Table 1. Three months later, with the volumes of the 3 treated node metastases diminished and the Tg level lower, no further ethanol ablation was performed. However, between 2013 and 2015, the serum Tg rose progressively (Fig. 1) from 3.4 to 11 ng/mL. No new suspicious node metastases were seen in 10/2015 on US and only ablated node metastases #3 and #4 were now identifiable and had no Doppler flow.

Further ethanol ablations and SM excisions (2015-2019)

In November 2015, the patient was examined by a local dermatologist, who noted a papular lesion in the right supraclavicular area and performed an excisional biopsy. The dermatopathologist concluded that it represented a cervical SM of PTC. On reassessment in January 2016, the patient's Tg had fallen to 8.2 ng/mL; an FDG PET-CT showed no evidence of FDG-avid malignancy, and no suspicious nodes were seen on US. The patient returned in February 2017, at which time his Tg had risen to 18 ng/mL. A chest CT scan revealed only a stable noncalcified 2- to 3-mm nodule in the right lung. Neck US revealed several nodes with suspicious features in right level IV. Additionally, the previously ablated node metastasis (#4) at level V had increased in volume from 17 to 94 mm^3 (Fig. 3). Three new node metastases (#6, #7, #8) in level IV were confirmed by USGB and in 2 sessions, one day apart, node metastases #4, #6, #7 and #8 were ablated (Table 1). When reassessed in June 2017, Tg was down to 2.4 ng/mL and 6 of the 8 ablated node metastases could not

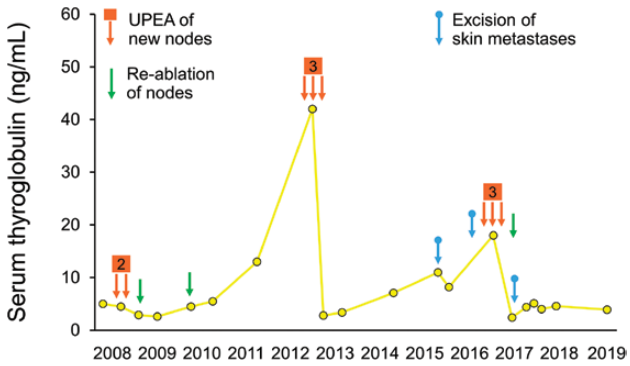

Figure 1. Changes in serum thyroglobulin, while on TSH suppression, and their correlation with the timing of each of the ethanol ablations and the excision of skin metastases during 2008-2019.

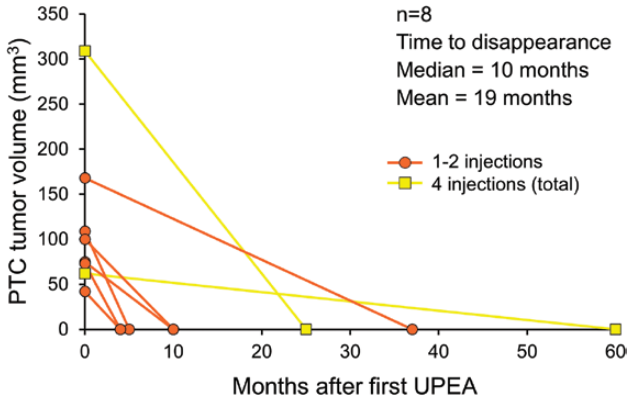

Figure 2. Time to disappearance on US of tumor in 8 ablated node metastases within the right neck.

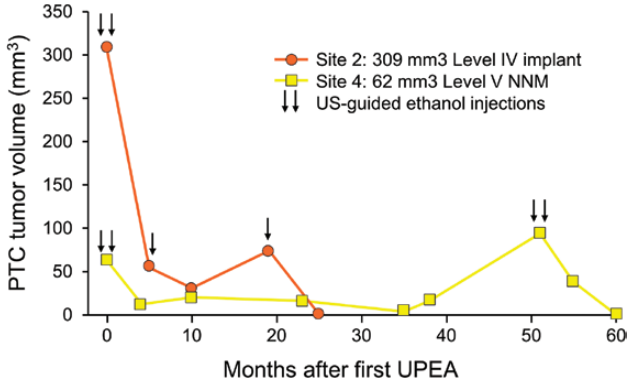

Figure 3. Time to disappearance of tumor in 2 nodal metastases requiring repeated (>2) ethanol injections to permit complete ablation.

be identified; #4 and #8 were identifiable but shrunken and avascular. No further ethanol ablation was recommended.

When patient returned for review in December 2017, a serum Tg had risen to 6.0 ng/mL and careful neck exam revealed, in a supraclavicular location, a barely palpable 5- to 6-mm subcutaneous nodule. A diagnostic US map (Fig. 4) demonstrated within the right neck the absence of the 8 previously ablated nodes but revealed 2 "indeterminate" areas in level V which were 5 and 4 mm in greatest dimension, appearing rather superficial and with marked color Doppler flow. The larger nodule underwent USGB and cytology was positive for PTC. Further ethanol ablation was considered but concerns were raised, because of the superficial nature of the SM that damage to the patient's overlying epidermis could ensue if ablation was to be performed. Accordingly, a dermatologic consultation was requested, and Mohs micrographic surgery was recommended for this presumed SM.

Under local anesthesia, the specimen was excised in a circular fashion through the full thickness of the dermis into the fat, using a 6-mm disposable punch. Histologic tumor-free margins were obtained in one stage (one block) by standard Mohs micrographic techniques. Final pathology confirmed PTC. Review at 6 months after Mohs resection found the serum Tg to be lower, at 4.6 ng/mL, but US demonstrated a persistent 4 × 5 × 5mm hypervascular nodule in level V close to the prior incision for Mohs surgery. This underwent USGB, was found to be PTC, and the dermatologic surgeon excised the lesion with a 1- to 2-mm clinically tumor-free margin in an elliptical fashion through the skin and the subcutaneous tissue. Dermatopathologic examination confirmed residual PTC and inked margins were free of tumor. More recently, the patient was evaluated in October 2018 and April 2019, when Tg levels were 4.3 and 3.9 ng/mL, respectively. During both recent visits neck US

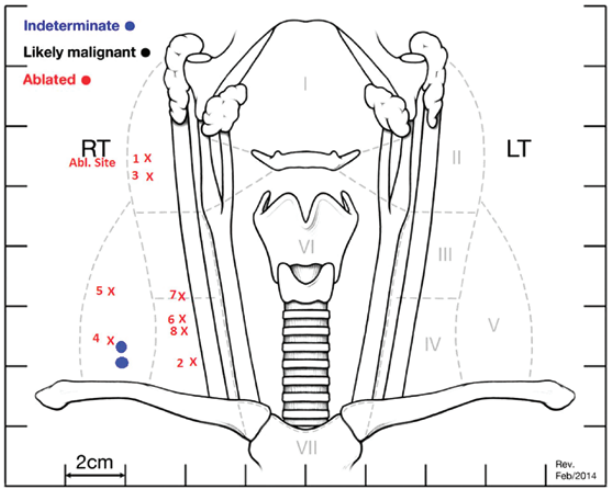

Figure 4. Copy of diagnostic ultrasound map of December 7, 2017, demonstrating within the right neck (levels II, IV, V) the anatomic sites of 8 previously ablated node metastases (denoted by the red crosses) and, additionally, 2 previously unidentified lesions (denoted by the blue ovals) considered to be SM within level V (labeled indeterminate since this map was created prior to positive USGB for PTC).

scanning revealed no evidence of persistent/recurrent PTC and a chest CT scan performed at 15 postoperative years revealed only stable punctate lung nodules.

Discussion

Haymart and colleagues [22] have stated that "the controversy in management of low-risk differentiated thyroid cancer (DTC) starts with the controversy in defining low-risk." Our patient at presentation in 2004 had an AGES score of 2.56 (>4 high risk), and a MACIS score of 4.08 (>6 high risk); he was also AMES low-risk [23]. However, because of his age at diagnosis (>45 years) and his N1b metastases, he was classified by the sixth edition of the AJCC/TNM staging system as stage IVA [24]. Fortunately, with the publication of the eigth edition of the AJCC/TNM staging system, his presenting stage would now be considered stage I, placing him within a low-risk category for all 4 prognostic systems [24, 25]. Thus, we should not be surprised that, despite 12 episodes of "recurrent" disease, our patient is surviving at 16 postoperative years and currently disease-free.

The first report describing the efficacy of ethanol ablation in treating selected node metastases in LRPTC patients was published in 2002, and concluded [26] that ethanol ablation "is a valuable treatment option for patients with limited cervical nodal metastases from PTC who are not amenable to further surgical or radioiodine therapy". In the 2009 American Thyroid Association (ATA) Management Guidelines [27], the authors stated that "Perhaps techniques will be developed to safely remove or destroy small cervical nodal metastases, which in some cases would otherwise progress to overt, clinically significant metastases". Contemporary ATA Guidelines [28] have emphasized that neck compartmental dissection remains the first-line therapy in DTC patients with clinically apparent or progressive node metastases. However, they did recognize a general consensus from studies and reviews [28] that ethanol ablation should be considered in patients who are poor surgical candidates or in patients refusing additional surgery. They also stated [28] that such "localized treatments… may be beneficial in patients with a single or a few metastases and in those with a high risk of local complications". Summarizing the reported literature through 2019 [11, 26, 29-34] on ethanol ablation of node metastases in PTC, Paz-Fumigalli concluded that ethanol ablation "appears to be less effective but safer than surgery, more effective in achieving biochemical control (Tg tumor marker) and safer than radiofrequency ablation" [35]. Moreover, as we

have emphasized in our earlier publications [10, 11, 26], ethanol ablation is also considerably cheaper than the conventional alternative of nodal dissection and does not require either general anesthesia or hospitalization.

When in 2013 we evaluated the long-term efficacy of ethanol ablation in controlling 52 "recurrent" node metastases in 25 PTC patients with advanced localized disease, we identified our treatment goals after a 20-year experience as "(i) elimination of significant nodal blood flow (tumor perfusion) by Doppler ultrasonography, (ii) reduction in volume of treated NNM, ideally to the point of disappearance on re-scanning, and (iii) when possible, concomitant reduction in circulating serum Tg levels on THST" [11]. In terms of our previously stated treatment goals [11] all 8 ablated node metastases had no tumor perfusion within 10 months of ethanol ablation and all disappeared within 60 months from first ethanol injection (Fig. 2). Moreover, when the patient presented to us in 2008, he had a serum Tg level of 4.8 ng/mL and by 2019 (at 15 postoperative years) he had a somewhat lower Tg level on TSH suppression of 3.9 ng/mL (Fig. 1), despite having had 11 biopsy-proven PTC "recurrences" during those years.

For our illustrative patient, Table I demonstrates that only the node metastasis (#2) first palpated prior to Mayo referral was >1 cm in diameter (estimated tumor volume 309 mm^3) and, thus, by current ATA Management Guidelines [28] would be considered to be a surgical target. The other 7 ablated nodal metastases ranged from 6 to 9 mm in greatest dimension (median 7 mm). Fig. 3 demonstrates the time taken (median 10 months) for the disappearance of each of the 8 ablated node metastases. Figure 4 demonstrates that node metastases #2 and #4 proved more difficult to manage and required each a total of 4 separate injections to achieve tumor disappearance.

Some might feel that the ablation of tiny persistent node metastases may represent overtreatment in LRPTC. However, considering the importance of patient input into shared decision making [2], it should be emphasized that our patient, when he presented to us in 2008, stated that he did not wish to undergo any further surgery requiring hospitalization and he wished to be informed promptly of the cytopathology of any new lesion found on neck imaging that would be amenable to USGB and if positive, further ethanol ablation.

It is well-recognized that thyroid cancer rarely metastasizes to the skin. During 1970-1996 only 6 patients with SM from thyroid cancer were seen at Mayo Clinic and 3 of these were PTC; all 3 showed evidence of dedifferentiation on biopsy [18]. All 3 PTC patients developed widely metastatic disease and 2 died within 3 months of the diagnosis of SM [18]. Our present patient is certainly unusual in having 3 SM in the context of stage I node-positive disease, developing his first SM at 13 years after presentation, and in 16 postoperative years to have at present no evidence of extracervical spread of his disease. We are familiar with a recent report [36] of the successful use of Mohs micrographic surgery in treating 2 SM involving the scalp in an 82 year old man with widely disseminated PTC. However, we believe that our patient is unique in having not only successful Mohs surgery, but 2 other successful excisions of SM performed in the setting of LRPTC localized to the neck. We are also delighted that his regional metastases were manageable by minimally invasive ethanol ablation and all "recurrent" events were satisfactorily managed by outpatient procedures under local anesthesia and without any associated morbidity.

In conclusion, we remain enthusiastic, after now a 3-decade experience, about the utility of ethanol ablation in LRPTC and concur with a recent conclusion from our colleagues in Florida [35] that "in properly selected patients with nodal metastases from DTC, compared with other locoregional therapy options, ethanol ablation has the greatest potential for applicability anywhere in the world because it does not require technology other than a sonographic unit, ethanol is widely available and inexpensive, the skills are easily taught and learned, and it is easily repeated with only local anesthetic".

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Additional information

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Data Availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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