Long-Term Efficacy of Lymph Node Reoperation for Persistent Papillary Thyroid Cancer

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Objective: The objective of the study was to determine the outcome of surgical resection of metastatic papillary thyroid cancer (PTC) in cervical lymph nodes after failure of initial surgery and I^{131} therapy.

Design: This was a retrospective clinical study.

Setting: The study was conducted at a university-based tertiary cancer hospital.

Patients: A cohort of 95 consecutive patients with recurrent/persistent PTC in the neck underwent initial reoperation during 1999–2005. All had previous thyroidectomy (±nodal dissection) and I^{131} therapy. Twenty-five patients with antithyroglobulin (Tg) antibodies were subsequently excluded.

Main Outcome Measures: Biochemical complete remission (BCR) was stringently defined as undetectable TSH-stimulated serum Tg.

Results: A total of 107 lymphadenectomies were undertaken in these 70 patients through January 2010. BCR was initially achieved in 12 patients (17%). Of the 58 patients with detectable postoperative Tg, 28 had a second reoperation and BCR was achieved in five (18%), seven had a third reoperation, and none achieved BCR. No patient achieving BCR had a subsequent recurrence after a mean follow-up of 60 months (range 4–116 months). In addition, two more patients achieved BCR during long-term follow-up without further intervention. In total, 19 patients (27%) achieved BCR and 32 patients (46%) achieved a TSH-stimulated Tg less than 2.0 ng/ml. Patients who did not achieve BCR had significant reduction in Tg after the first ($P < 0.001$) and second ($P = 0.008$) operations. No patient developed detectable distant metastases or died from PTC.

Conclusions: Surgical resection of persistent PTC in cervical lymph nodes achieves BCR, when most stringently defined, in 27% of patients, sometimes requiring several surgeries. No biochemical or clinical recurrences occurred during follow-up. In patients who do not achieve BCR, Tg levels were significantly reduced. The long-term durability and impact of this intervention will require further investigation. **(*J Clin Endocrinol Metab* 95: 2187–2194, 2010)**

Papillary thyroid cancer (PTC), the most common of the well-differentiated thyroid cancers, accounts for about 80–85% of follicular cell-derived thyroid cancers in developed countries in which sufficient iodine is present in the diet (1). Local recurrences are found in 5–20% of patients with PTC, two thirds of which are localized to cervical lymph nodes (2). The 10-yr relative survival rate for individuals with PTC in the United States is 93% (3). Still, more than half of the deaths from thyroid cancer are caused by PTC due to its comparatively high frequency (3).

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Abbreviations: ATA, American Thyroid Association; BCR, biochemical complete remission; FDG-PET, flourodeoxyglucose positron emission tomography; FNA, fine-needle aspiration; LNM, lymph node metastasis; MRND, modified radical neck dissection; PTC, papillary thyroid cancer; rhTSH, recombinant human TSH; Tg, thyroglobulin; US, ultrasound.

PTC patients are typically treated with total thyroidectomy and therapeutic lymph node dissection if nodal metastases are grossly identified, followed by radioactive iodine ablation and TSH suppression using L-thyroxine for larger, invasive, or metastatic tumors (4). The role of prophylactic central compartment neck dissection remains controversial (5). For patients treated with total thyroidectomy and radioiodine in whom all normal thyroid tissue has been removed and/or ablated, the cornerstones of surveillance for disease recurrence or progression are measurement of serum thyroglobulin (Tg) and neck ultrasound (US) (5). In the absence of interfering anti-Tg antibodies that occur in 15–20% of patients, Tg monitoring accurately detects residual, recurrent, and/or progressive disease (4). Tg expression and release are stimulated by TSH. Measurement of serum Tg during TSH suppression therapy is used to monitor patients, and if positive, the test is highly specific. Thus, patients with detectable serum Tg during TSH suppression on L-thyroxine or measurable Tg after TSH stimulation (especially if >2 ng/ml) are highly likely to harbor residual tumor (5, 6). TSH stimulation greatly enhances the sensitivity of Tg monitoring and can be achieved using either thyroid hormone withdrawal or recombinant human TSH (rhTSH) (4). An undetectable TSH-stimulated Tg level reliably predicts the absence of thyroid cancer (7).

High resolution US can be used to identify patients with nonpalpable neck lymph node metastases (LNMs) (4, 8, 9). Suspicion for disease in the neck by US in the absence of distant metastases indicates a potentially surgically curable patient. Several previous studies have suggested that 19–71% of these patients can be rendered free of disease with additional surgery, although the criteria used to determine postoperative clinical status and the durations of follow-up are inconsistent between studies (10–14). Surgeons historically avoided neck lymph node dissection for recurrent/persistent PTC in absence of clinically palpable disease. This approach was likely derived from the controversial significance of resected LNMs at presentation in PTC (8, 9) and the limited sensitivities of older Tg assays and imaging techniques. However, most studies agree that LNMs at presentation do predict subsequent disease recurrence (9, 15), and the studies of LNMs at presentation do not definitively address the potential subsequent impact of the LNMs that are refractory to initial therapy. These refractory metastases may cause morbidity and mortality if allowed to progress. Indeed, long-term cancer mortality rates up to 16% have been reported when the initial tumor recurrence was in cervical lymph nodes or in the contralateral thyroid (9, 16). Furthermore, several nonrandomized series demonstrated that some patients with persistent disease after therapy for persistent/recurrent cervical lymph node disease have adverse outcomes including about 20% with tumor progression or distant metastases, and some patient deaths have been reported despite relatively short follow-up. Conversely, the vast majority of those surgically rendered free of disease reportedly remained in remission (10, 12).

The enhanced ability to detect and localize small amounts of persistent and/or recurrent thyroid cancer using serum Tg measurement and modern imaging modalities changed recommended practice patterns to include early consideration of surgical resection with curative intent. Indeed, in recent years the National Comprehensive Cancer Network and the American Thyroid Association (ATA) guidelines prefer surgery (if resectable) for patients with locoregional PTC recurrence (17, 18). Despite these recommendations and changes in clinical practice, the results of this approach have not been systematically studied. The object of this study was to determine the outcome of patients who underwent potentially curable surgery, the durability of the response, and whether any criteria could predict which patients would benefit from an aggressive surgical approach to locoregional recurrence after failure of initial therapy including thyroidectomy and radioactive iodine ablation.

Patients and Methods

Patients

Patients treated at the Arthur G. James Cancer Hospital and Richard J. Solove Research institute at The Ohio State University for locally recurrent/persistent PTC in the absence of distant metastases during 1999–2005 were retrospectively identified with exempt research approval of the institutional review board. There was no minimum or maximum size of the metastatic lymph node(s) chosen *a priori* to be removed. Distant metastases were excluded by preoperative chest x-ray in all patients and chest computed tomography when the basal or TSH-stimulated serum Tg was greater than 2 ng/ml. A minority of patients underwent other imaging such as fluorodeoxyglucose positron emission tomography (FDG-PET), bone scan, or extracervical magnetic resonance imaging. Medical charts were reviewed for age, gender, capsule invasion, tumor size, lymph node involvement, stage at thyroidectomy, preoperative Tg levels (unstimulated, stimulated, and method of stimulation), method by which recurrence was detected, number of US-guided fine-needle aspirations (FNAs) performed, the preoperative total dose of radioactive iodine, number and type of neck compartments dissected, number of lymph nodes resected, number of lymph nodes with PTC, postoperative Tg levels (unstimulated, stimulated, and method of stimulation), operative complications, disease-free interval, and total duration of follow-up.

Between May 1999 and May 2005, 95 consecutive patients with recurrent or persistent PTC in the neck underwent exploration by the same surgeon (W.B.F.). Twenty-five patients with anti-Tg antibodies were excluded from analysis because these antibodies interfere with reliable serum Tg measurement so that the subsequent state of their disease cannot be biochemically established.

TABLE 1. Demographics of 70 patients and risk factors

Gender	Male	Female
Number	22	48
Age at diagnosis of PTC (yr)	Median 35 (15–71)	
Age at first neck reexploration (yr)	Median 41 (18–73)	
Time from thyroidectomy to first neck reexploration (yr)	Median 3 (<1–24)	
Age 40 yr or younger	10	38
Age older than 40 yr	12	10
Stage I at thyroidectomy[a]	17	43
Stage III at thyroidectomy[a]	5	5
Tumor size less than 4 cm	18	43
Tumor size greate than 4 cm	2	2
Tumor size unknown	2	3
Capsule invasion	13	29
Capsule invasion unknown	0	4
No capsule invasion	9	15
Positive LN at thyroidectomy	15	37
Normal LN at thyroidectomy	6	10
Not known	1	1
Preoperative radioactive iodine (mCi)	Median 217 (29–995)	
Post-RO THW stimulated TSH	Median 59.5 (13.9–332)	
Post-RO rhTSH stimulated TSH[b]	Median 13.4 (1.2–88)	

RO, Reoperation; LN, lymph node.

[a] Staging classification published elsewhere (20).

[b] Seventy-two hours after the second rhTSH injection.

The remaining 70 patients (Table 1) underwent at total of 96 neck explorations through May 2005, and then the cohort was followed up through January 2010. Eight patients (patients 14, 19, 37, 76, 83, 91, 92, 100) underwent an additional 11 reoperations, including one for BCR (patient 14). In total, they underwent a total of 107 neck explorations based on an elevated basal or stimulated Tg plus malignant cytology on FNA (n = 48) or anatomically defined neck lesions on high-resolution US suspicious for recurrent PTC without FNA (n = 55), palpable cervical lymphadenopathy without FNA (n = 2), or FDG-PET scan without FNA (n = 2). Office-based neck US was performed to inspect the superior mediastinum, bilateral central, and bilateral lateral neck compartments. US features that suggested malignancy (alone or in combination) included loss of the fatty hilum, a rounded shape, calcifications, cystic changes, or hypoechogenicity.

All patients had previously undergone total thyroidectomy (with or without lymph node dissection) and had failed at least one treatment with radioactive iodine. Upon reoperation, lymph node dissections were performed as either a unilateral or bilateral central neck dissection (level VI; n = 49); a unilateral modified radical neck dissection (MRND; levels II-V; n = 22); combined unilateral MRND or focused lateral node dissection or posterior neck dissection and central neck dissection (n = 14); focused node dissection when a formal neck dissection had previously been performed (n = 12), bilateral MRND, or unilateral MRND plus focused contralateral neck dissection (n = 7); simple lymph node excision (n = 2); or video-assisted thoracoscopic surgery (n = 1, Table 2). The definitions of the cervical compartments, the extent of their dissection, and the rational for compartmental neck dissections (as opposed to berry picking procedures) were as previously described (17, 19). The carotid artery, jugular vein, vagus, phrenic, spinal accessory, and brachial plexus nerves were spared unless they were involved by disease.

Tg measurements

All serum Tg measurements were performed by the same laboratory using the same method for each individual patient for a given surgery, although more than one Tg assay was used between patients. Using the Nichols chemiluminescence immunometric assay (Nichols Institute Diagnostics; catalog no. 60-4240, analytical sensitivity 0.07 ng/ml, functional sensitivity 0.5 ng/ml), the interassay coefficients of variation for four serum pool controls (0.44, 1.49–2.29, 3.93–6.01, and 18.10–21.90 ng/ml) were 24.8, 10.6, 10.5, and 4.8%, respectively. The reference range for normal subjects with an intact thyroid was 3.2–57.7 ng/ml, with a mean of 13.5 ng/ml. To exclude a hook affect, all samples were analyzed undiluted and with a 1:10 dilution. If the undiluted value was greater than 100 ng/ml, additional dilutions were analyzed. The reported value was the average of all values that were detectable but less than 100 ng/ml. Using the Nichols Advantage Tg assay (Nichols Institute Diagnostics, catalog no. 62-7035, analytical sensitivity $\leq$0.04 ng/ml, functional sensitivity $\leq$0.3 ng/ml), the interassay coefficients of variation for four serum pool controls (0.60, 1.88, 47.4, and 179 ng/ml) were 16.8, 5.9, 3.2, and 4.0%, respectively. The intraassay coefficients of variation for three serum pool controls (1.8, 47.8, and 174 ng/ml) were 2.2, 2.1, and 3.6%, respectively. The normal range was 4.0–40 ng/ml, with a mean of 16.8 ng/ml. The minimum value reported was 0.9 ng/ml. A similar strategy using undiluted and diluted samples was performed to exclude a hook effect with this assay. All values that were detectable but less than 60 ng/ml were used to determine the average value that was subsequently reported. Using both assays, serum samples were frozen and reassayed with the latest Tg sample if deemed necessary due to inconsistent results.

Biochemical complete remission (BCR) was defined using the strict criteria of no detectable Tg with stimulation by T_4 withdrawal or rhTSH.

Statistics

Univariate logistic regression was used to test potential predictors of BCR. Wilcoxon signed rank tests were performed to assess within-patient change in unstimulated Tg from before to after operation in patients in whom a BCR was not achieved. Fisher's exact tests were used to compare the proportion of patients in whom a BCR was achieved for patients with detectable unstimulated preoperation Tg *vs.* patients with preoperation Tg detectable only with stimulation. A significance level of $\alpha = 0.05$ was used for all tests.

Results

Patients were predominantly female with a median of 3 yr from thyroidectomy to neck exploration for recurrent or residual disease (Table 1). The majority of patients had LNM during initial thyroidectomy and the majority had thyroid capsule penetration by the tumor (Table 1). All patients had at least one treatment of radioactive iodine (that included a posttreatment whole body scan) with a median cumulative dose of 217 mCi per patient.

Surgical outcome

A total of 107 lymphadenectomies were undertaken in 70 anti-Tg antibody-negative patients between May 1999

TABLE 2. Patients with biochemical evidence of disease and negative surgical histology at reoperation (RO)

Patient	Surgical indication	Largest target lesion[a]	RO (n)/total RO (n)	Comment and target lesion follow-up	Eventual BCR
1	Palpation	10 mm	1/2	Target resected; 0/1+ LNs	No
4	US FNA+ (twice)	8 × 8 mm	2/2	0/6+ LNs resected; F/U US confirmed unresected target; repeat US FNA−	No
19	Palpation	10 mm	2/4	Target resected 0/1+ LNs; prior US considered the target benign	No
22	FDG-PET	SUV 4.5	1/2	LNs with sinus histiocytosis; 0/22+ LNs	No
25	US FNA+	10 × 4 × 7 mm	2/2	Unstimulated Tg dropped from 2.2 to <0.5 postoperatively despite 0/13+ LNs; target not seen on F/U US	No
29	US FNA+	11 × 8 mm	1/1	0/3+ LNs resected; no F/U US	No
59	US	6 × 5 mm	2/2	FNA deferred because target was surrounded by vascular structures; 0/5+ LNs; target not seen on F/U US	No
62	US FNA+	6 × 6 mm	2/2	Surgery stopped because dense adhesions prohibited safe dissection; F/U US confirmed unresected target	No
85	US	8 × 7 mm	1/1	No F/U US	No
91	US	18 × 12 mm, subclavicular mass	2/3	Tumor not found by thoroscopy; repeat US+; third RO resected 2/3+ LNs	No

F/U, Follow-up; LN, lymph nodes.

[a] US dimensions are width × depth in transverse view or craniocaudal length × depth × width.

and January 2010. Overall, there were 10 lymphadenectomies (9%) that failed to identify recurrent PTC based on US with selective use of FNA (n = 7), palpation (n = 2), and FDG-PET (n = 1) (Table 2). Neck US with selective use of FNA was performed in 102 of 107 cases before lymphadenectomy with FNA performed in 47% (48 of 102) and accurately identified recurrent PTC in 95 of 102 cases (93%) using the strict definition of positive surgical histology. However, four of the seven patients with positive US findings and negative surgical histology had a positive preoperative US-FNA (Table 2). One of these four (patient 25) had a preoperative serum Tg of 2.2 ng/ml during TSH suppression that reduced to less than 0.5 ng/ml postoperatively despite the negative operative histology. Another patient (no. 4) with positive preoperative US-FNA cytology (twice) and negative surgery had the lesion still present on postoperative US, and in one patient it was decided intraoperatively that the lesion could not be resected safely due to dense adhesions (patient 62). One patient with a positive US (but no FNA) had subsequent positive surgical histology of the same target lesion at her third reoperation (patient 91). When considering all reoperations, if one considers malignant surgical histology or malignant US-FNA cytology as positive, then neck US with selective use of US-FNA accurately identified recurrent PTC in 100 of 102 lymphadenectomies (98%).

The median number of lymph nodes removed after the first reoperation was 11 (range 1–61) with median positive PTC histology in two (range 0–11); after the second reoperation, the median number of lymph nodes removed was seven (range 0–55) with median positive histology in two (range 0–12), and after the third reoperation, the median number of lymph nodes removed was three (range 1–34) with median positive histology in two (range 1–5). The total number of nodes removed, as well as the number of positive nodes, was similar between those patients who achieved BCR *vs.* those with persistent disease (data not shown). The median number of nodes harvested for the cases in whom pathology did not reveal recurrent PTC was four (range 0–22).

No patients developed new long-term hypoparathyroidism or recurrent laryngeal nerve injury. One patient (1%; no. 105) had a chyle leak at the second reoperation and was reexplored with successful ligation of the thoracic duct but did not achieve BCR.

Biochemical complete remission

Overall biochemical complete remission

During long-term follow-up, patients 12 and 101 (both stage I) who initially had detectable postoperative stimulated Tg values (0.5 and 1.2 ng/ml, respectively) after their first reoperations both subsequently became BCR to repetitive stimulated Tg testing that has persisted 6.8 and 3.5 yr, respectively, with negative neck US examinations despite L-thyroxine as the only interval treatment since reoperation. This delayed BCR is not included in the analyses for prompt postoperative BCR described below or in Table 3 and may reflect the results of both surgery and late effects of their last radioiodine therapies 10.8 and 3.8 yr

TABLE 3. Reoperation (RO) rate of prompt BCR using various stimulated Tg cutoff values[a]

Postoperative stimulated Tg	First RO n = 70) (% surgeries)	Second RO (n = 28) (% surgeries)	Third RO (n = 7) (% surgeries)	Fourth RO (n = 2) (% surgeries)	BCR with all RO (% patients)
Tg undetectable[b]	12 (17%)	5 (18%)	0 (0%)	0 (0%)	17 (24%)
Tg <1 ng/ml	16 (23%)	5 (18%)	0 (0%)	0 (0%)	20 (29%)[c]
Tg <2 ng/ml	24 (34%)	8 (29%)	1 (14%)	0 (0%)	32 (46%)[c]

[a] Excludes patients 12 and 101 as described in the text.

[b] Undetectable means less than 0.5 ng/ml when the Nichols chemiluminescence immunometric assay was used (catalog no. 60-4240) and less than 0.9 ng/mL when the Nichols Advantage Tg assay (catalog no. 62-7035) was used.

[c] Does not total the sum achieved in reoperations 1–4 because patient 14 is counted only once. Despite her stimulated Tg of 0.5 ng/ml after the first reoperation, she developed new suspicious lymph nodes during US follow-up and underwent a second reoperation with a right central neck dissection 6.7 yr after her initial reoperation with five of 18 resected lymph nodes involved with PTC and a subsequent prompt BCR that has been durable for 21 months.

before developing BCR, respectively. These patients are included, however, in the total of 19 of 70 patients (27%) in this series that achieved overall BCR.

Prompt postoperative biochemical complete remission

Before the first reoperation, the mean basal Tg of the cohort was 8.4 ng/ml and median 4.0 ng/ml (range undetectable to 100.5 ng/ml). As summarized in Table 3, BCR was promptly achieved postoperatively in 12 of 70 patients (17%) after the first reoperation. For these 12 patients, the mean basal Tg was 12.5 ng/ml and median 4.2 ng/ml (range undetectable to 100.5 ng/ml) before the first reoperation. Of the remaining 58 patients with detectable postoperative Tg, 28 went on to a second reoperation with prompt BCR being achieved in five (18%). Before the second reoperation, the mean basal Tg of the cohort was 9.1 ng/ml and median 1.3 ng/ml (range undetectable to 99.1 ng/ml). For the five patients who achieved BCR, the mean and median basal Tg was undetectable (range undetectable to 1.2 ng/ml) before the second reoperation. Before the third reoperation, the mean basal Tg of the cohort was 23.8 ng/ml and median 4.5 ng/ml (range undetectable to 116.0 ng/ml). Third reoperations were performed in seven patients and none resulted in BCR. The mean and median basal Tg level before the first reoperation in patients who experienced a prompt BCR with any reoperation was 9.7 and 2.7 ng/ml, respectively (range undetectable to 100.5 ng/ml). Patients in whom a prompt BCR was not achieved in that operation had significant reductions in unstimulated Tg levels after both the first reoperation (median decrease 1.7 ng/ml, interquartile range 0.3–7.4 ng/ml, $P < 0.001$) and the second reoperation (median decrease 0.8 ng/ml, interquartile range 0–2.2 ng/ml, $P = 0.008$). The median decrease in unstimulated Tg after the third reoperation was 0.7 ng/ml (interquartile range 0–6.2 ng/ml, $P = 0.06$).

In total, BCR was achieved promptly after 17 of 107 surgical procedures (16%), leading to prompt postoperative BCR in 17 of 70 patients (24%). Sixteen patients who achieved prompt BCR [(16 of 17) 94%] were tumor, node, metastasis stage I, and the remainder was stage III (20). Using alternative stimulated serum Tg cutoff values, the yield of reoperations are shown in Table 3. For example, using a TSH-stimulated Tg level of less than 2.0 ng/ml as a cut point, 46% of patients would be classified as having a BCR after all reoperations. Because some of the patients with TSH-stimulated Tg levels between 0.5 and 2.0 ng/ml will develop recurrent PTC (6), the most stringent definition (TSH stimulated Tg undetectable) was used for all BCR analyses noted below.

Prompt BCR was achieved after the first reoperation in five of 15 patients (33%) when the preoperative Tg was detected only by stimulation compared with seven of 55 patients (13%) when Tg was detected without stimulation ($P = 0.11$). In patients who underwent a second reoperation, prompt BCR was achieved in three of eight patients (38%) when Tg was detected only with stimulation compared with two of 20 patients (10%) when preoperative Tg was detected without stimulation ($P = 0.12$). When evaluating all patients after all surgical procedures, prompt BCR was achieved in five of 15 people (33%) when the preoperative Tg before their first reoperation was detected only by stimulation compared with 12 of 55 people (22%) when Tg before the first reoperation was detected without stimulation ($P = 0.50$, Fisher's exact test).

The independent variables of age at initial PTC diagnosis, gender, capsule invasion by the primary tumor, primary tumor size, lymph node involvement, TNM stage at thyroidectomy, age at first reoperation, years between initial PTC surgery and reoperation, detectable *vs.* undetectable unstimulated Tg level before reoperation, magnitude of the preoperative unstimulated Tg level, number of nodes harvested, one *vs.* more than one resected metastatic lymph nodes at reoperation, number of nodes containing PTC during lymphadenectomy, the presence of disease in

the central *vs.* the lateral neck, disease in more than one nodal compartment, and the number of nodal compartments reoperated were evaluated on a per-patient basis by univariate analysis to determine predictors of BCR. None were significantly associated with BCR.

Long-term follow-up

Overall mean follow-up time for patients achieving prompt postoperative BCR was 60 months (range 4–116 months) after surgery, during which time no patient demonstrated evidence of biochemical or clinical recurrence.

During long-term follow-up through January 2010, 10 of the 53 patients who did not achieve prompt BCR were not tested for distant metastases, whereas the remaining 43 patients evaluated by chest computed tomography in 36, chest radiograph in 20, skeletal imaging (bone scan or magnetic resonance imaging) in five, whole-body FDG-PET in eight, or follow-up undetectable stimulated Tg in the absence of anti-Tg antibodies in patients 12 and 101 who became BCR. No distant metastases or deaths from thyroid cancer were identified after a median of 3.9 yr from their first reoperation until their last test for distant metastases (range 0.2–8.9 yr). Patient 92 was treated with external beam radiation therapy for progressive FDG-avid cervical and upper mediastinal lymphadenopathy that progressed despite four reoperations and sorafenib therapy (21).

Discussion

PTC is usually an indolent and potentially curable form of differentiated thyroid carcinoma (4). However, some PTC patients recur at local sites and less often distant locations, whereas some patients eventually die of their disease (3). Studies from our institution have shown that radioactive iodine as part of initial therapy with remnant ablation or treatment reduces cancer recurrence and mortality (9). However, the effectiveness of radioiodine or surgery against persistent/recurrent disease in cervical lymph nodes is less certain. Most patients with PTC have a negative follow-up diagnostic radioiodine scan after initial ablation, regardless of their disease status (7). Patients with residual disease despite a negative diagnostic whole-body radioiodine scan may not benefit from additional radioiodine treatment, and our experience has been that surgical intervention is more likely to render them free of disease than is empirical radioiodine therapy (6). This goes against the once-common belief that recurrent PTC in the neck is readily ablated by radioiodine therapy. Although we did not randomize these patients to surgery *vs.* additional radioiodine treatment, we submit that their disease had already survived prior radioiodine treatment (median cumulative activity of 217 mCi) and was likely to do so again and therefore were classified as having radioiodine nonresponsive PTC.

In this cohort of patients, we adopted an approach of aggressive detection of recurrent/persistent PTC including stimulated Tg by L-thyroxine withdrawal or rhTSH after initial disease resection and radioiodine ablation in patients with undetectable basal Tg during L-thyroxine therapy. High-resolution US was performed by experienced thyroid cancer clinicians in most cases (99 of 104) before lymphadenectomy to detect nonpalpable disease in the neck. All US descriptive reports included the size and number of the suspicious lesion(s), the compartment(s) involved, and their location(s) in reference to fixed structures like the clavicle, trachea, carotid and jugular vessels, or angle of the mandible. Occasionally the suspicious lymph node site(s) was marked immediately preoperatively on the skin to help guide the surgeon to the target(s). This was most commonly performed in patients undergoing lymph node dissection after MRND had been previously performed.

US-FNA of suspicious lymph nodes was more commonly performed initially in our series. As we gained more confidence in US imaging, FNA was performed more selectively as the result became less likely to alter patient management. Thus, 53% of the lymphadenectomies performed based on a suspicious US examination were done without cytological confirmation. Using this selective US-FNA approach, only three of our patients (no. 59, 85, 91) in whom US-FNA was foregone had negative surgical pathology (Table 2). In patient 59 the lesion was deemed inaccessible to FNA, in patient 85 a postoperative US was not performed to confirm that the target lesion was actually resected, and in patient 91 a subsequent surgery confirmed that the target lesion was tumor. US with selective use of US-FNA detected recurrent PTC (as witnessed by positive postoperative histology) in 93% of lymphadenectomies, which is comparable with the study from Mayo Clinic (8) in which US had a positive predictive value of 94% in reoperative PTC. Our rate of US detection rose to 98% if patients with positive FNA cytology or subsequent surgical histology are also counted as positive. These findings demonstrate the superior sensitivity of neck US over physical examination and support the recommendations of the ATA, which emphasize the role of neck US in the follow-up of patients with PTC (5, 17).

Whereas surgery failed to detect recurrent PTC in 10 lymphadenectomies (9%), including five with suspicious US-FNA cytology or subsequent positive surgical histology (Table 2), this result is comparable with other series that required diagnostic preoperative US-FNA (8, 11) and

likely reflects the high sensitivity of US as well as the operative challenge of finding small malignant lymph nodes in patients undergoing reoperation. This operative challenge combined with the risk of operative harm, strong potential for persistent postoperative disease, and unknown impact on long-term survival is reflected in the 2009 ATA guidelines that recommend follow-up without surgical intervention of small lymph nodes (5).

When defined stringently, BCR was achieved in 14 patients (20%) after the first neck exploration: 12 promptly and an additional two patients during long-term follow-up without further intervention. In addition to these patients, five additional patients achieved BCR after a second exploration. In total, BCR was achieved in 19 of the cohort (27%) through January 2010. Those in whom a BCR was not achieved had a significant reduction in their Tg levels postoperatively, consistent with tumor debulking. Whether patients benefit from tumor reduction in the absence of BCR is unknown, and whether their residual disease resides in undiagnosed local and/or distant sites remains to be established. Furthermore, the optimal definition of BCR that best correlates with clinical outcomes will require extended long-term follow-up of this cohort.

The significance that 18 of 61 stage I patients (30%) may enter BCR after reoperation may be questioned by some because of the typically excellent prognosis of these low-risk patients. However, the fact that one of 10 stage III patients (10%) also entered BCR after reoperation suggests that although the rate of BCR may diminish with advancing stage, at least some patients at higher risk disease may benefit from this intervention.

Other studies have indicated that reoperation in the neck carried a 20% morbidity (22), usually in the form of recurrent laryngeal nerve paralysis or hypoparathyroidism. In this study we had no new recurrent nerve paralysis or hypoparathyroidism, and others have demonstrated that reoperation of the central compartment can be done with acceptable morbidity (14, 23). We did have one patient develop a chyle leak that was recognized early, and the thoracic duct was ligated immediately postoperatively. Thus, in the hands of an experienced thyroid cancer team, 27% patients with residual PTC confined to the neck and upper mediastinum may be rendered biochemically free of disease. None of these patients has relapsed during follow-up. These results must be considered in the context of a 73% chance that some reduced amount of residual disease will persist.

Conclusion

PTC is the most common form of differentiated thyroid cancer. Surgical resection of locally recurrent or persistent radioactive iodine-resistant PTC can be achieved in experienced hands with no mortality and relatively low morbidity. BCR was achieved in 27% of patients who were unlikely to be cured otherwise. The ultimate impact of this approach on long-term outcome and disease-free survival is yet to be determined.

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Disclosure Summary: O.A.-S., W.B.F., M.B., and K.P. have nothing to declare. M.D.R. has served as coinvestigator on clinical trials sponsored by Diagnostic Hybrids Inc., Eisai Inc., Exelixis, and Daiichi Sankyo and will serve on an advisory board for Veracyte, Inc. R.T.K. has served as an unpaid consultant for Genzyme Corp.

References

1. **Jossart GH, Clark OH** 1994 Well-differentiated thyroid cancer. Curr Probl Surg 31:933–1012
2. **Schlumberger MJ** 1998 Medical progress—papillary and follicular thyroid carcinoma. N Engl J Med 338:297–306
3. **Hundahl SA, Fleming ID, Fremgen AM, Menck HR** 1998 A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985–1995. Cancer 83:2638–2648
4. **Kloos RT** 2005 Papillary thyroid cancer: medical management and follow-up. Curr Treat Options Oncol 6:323–338
5. **Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM** 2009 Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 19:1167–1214
6. **Kloos RT, Mazzaferri EL** 2005 A single recombinant human thyrotropin-stimulated serum thyroglobulin measurement predicts differentiated thyroid carcinoma metastases three to five years later. J Clin Endocrinol Metab 90:5047–5057
7. **Mazzaferri EL, Kloos RT** 2002 Is diagnostic iodine-131 scanning with recombinant human TSH useful in the follow-up of differentiated thyroid cancer after thyroid ablation? J Clin Endocrinol Metab 87:1490–1498
8. **Stulak JM, Grant CS, Farley DR, Thompson GB, van Heerden JA, Hay ID, Reading CC, Charboneau JW** 2006 Value of preoperative ultrasonography in the surgical management of initial and reoperative papillary thyroid cancer. Arch Surg 141:489–494; discussion 494–496
9. **Mazzaferri EL, Kloos RT** 2001 Clinical review 128: current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 86:1447–1463
10. **Alzahrani AS, Raef H, Sultan A, Al Sobhi S, Ingemansson S, Ahmed M, Al Mahfouz A** 2002 Impact of cervical lymph node dissection on serum TG and the course of disease in TG-positive, radioactive iodine whole body scan-negative recurrent/persistent papillary thyroid cancer. J Endocrinol Invest 25:526–531
11. **Binyousef HM, Alzahrani AS, Al-Sobhi SS, Al SH, Chaudhari MA, Raef HM** 2004 Preoperative neck ultrasonographic mapping for persistent/recurrent papillary thyroid cancer. World J Surg 28:1110–1114
12. **Davila-Cervantes A, Gamino R, Gonzalez O, Herrera MF** 2003

Surgical treatment of recurrent differentiated thyroid carcinoma. Eur J Surg Suppl 14–17

13. **Clayman GL, Shellenberger TD, Ginsberg LE, Edeiken BS, El-Naggar AK, Sellin RV, Waguespack SG, Roberts DB, Mishra A, Sherman SI** 2009 Approach and safety of comprehensive central compartment dissection in patients with recurrent papillary thyroid carcinoma. Head Neck 31:1152–1163
14. **Schuff KG, Weber SM, Givi B, Samuels MH, Andersen PE, Cohen JI** 2008 Efficacy of nodal dissection for treatment of persistent/recurrent papillary thyroid cancer. Laryngoscope 118:768–775
15. **Grebe SK, Hay ID** 1996 Thyroid cancer nodal metastases: biologic significance and therapeutic considerations. Surg Oncol Clin N Am 5:43–63
16. **Grant CS, Hay D** 1988 Local recurrence of papillary thyroid carcinoma after unilateral or bilateral thyroidectomy. Wien Klin Wochenschr 100: 342–336
17. **Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Sherman SI, Tuttle RM** 2006 Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 16:109–142
18. **Sherman SI, Angelos P, Ball DW, Byrd D, Clark OH, Daniels GH, Dilawari RA, Ehya H, Farrar WB, Gagel RF, Kandeel F, Kloos RT, Kopp P, Lamonica DM, Loree TR, Lydiatt WM, McCaffrey J, Olson Jr JA, Ridge JA, Shah JP, Sisson JC, Tuttle RM, Urist MM** 2007 Thyroid carcinoma. J Natl Compr Canc Netw 5:568–621
19. **Robbins KT, Medina JE, Wolfe GT, Levine PA, Sessions RB, Pruet CW** 1991 Standardizing neck dissection terminology. Official report of the Academy's Committee for Head and Neck Surgery and Oncology. Arch Otolaryngol Head Neck Surg 117:601–605
20. **Greene FL, Page DL, Fleming ID, Fritz A, Balch CM** 2002 AJCC cancer staging manual. 6th ed. Chicago: Springer Verlag
21. **Kloos RT, Ringel MD, Knopp MV, Hall NC, King M, Stevens R, Liang J, Wakely Jr PE, Vasko VV, Saji M, Rittenberry J, Wei L, Arbogast D, Collamore M, Wright JJ, Grever M, Shah MH** 2009 Phase II trial of sorafenib in metastatic thyroid cancer. J Clin Oncol 27:1675–1684
22. **Mazzaferri EL, Young RL, Oertel JE, Kemmerer WT, Page CP** 1977 Papillary thyroid carcinoma: the impact of therapy in 576 patients. Medicine (Baltimore) 56:171–196
23. **Kim MK, Mandel SH, Baloch Z, Livolsi VA, Langer JE, Didonato L, Fish S, Weber RS** 2004 Morbidity following central compartment reoperation for recurrent or persistent thyroid cancer. Arch Otolaryngol Head Neck Surg 130:1214–1216