Persistent cervical PTC lymph-node metastases may require several surgical resections to achieve biochemical or clinical evidence of disease-free outcome

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SUMMARY

BACKGROUND

Papillary thyroid cancer (PTC) is the most common form of thyroid cancer, comprising about 80% of thyroid cancers. Although thyroid cancer generally has a good prognosis, about 7% of patients die from this tumor within 10 years after the diagnosis of PTC. Local recurrences are found in 5 to 20% of patients with this disease, about 60% of which are localized to cervical lymph-node metastases. The objective of this study was to determine the outcome of surgical resection of metastatic PTC in cervical lymph-node metastases

METHODS

This is a retrospective study of 95 consecutive patients with cervical-lymph-node recurrence or persistent PTC treated at the Arthur G. James Cancer Hospital and Richard J. Solove Research institute at Ohio State University from 1999 through 2005. Lymph-node metastases of all sizes were chosen for surgical excision. Excluded from the study were patients with distant metastases identified by preoperative chest x-ray in all patients and by chest computed tomography (CT) when basal or TSH-stimulated serum thyroglobulin (Tg) was >2ng/ml. A minority of patients had 18-fluorodeoxyglucose positron-emission tomography (18FDG-PET), bone scans or extracervical magnetic resonance imaging (MRI).

Data were extracted from medical records and reviewed for the following variables: patient age, sex, tumor capsule invasion and tumor size, lymph-node metastases, and tumor stage at the time of thyroidectomy. Recurrence was identified by preoperative Tg, both unstimulated and TSH-stimulated, postoperative Tg levels, and ultrasound (US)-guided fine-needle aspiration biopsies (FNABs). The total amount of radioiodine (^{131}I) administered preoperatively, and the number and type of neck lymph-node compartments dissected, the number of lymph nodes with PTC resected, surgical complications, disease-free intervals, and total duration of follow-up were also extracted.

Between May 1999 and May 2005, 95 consecutive patients with recurrent or persistent PTC neck metastases were performed by the same surgeon. Excluded from the analysis were 25 patients with anti-Tg antibodies (TgAb). All serum Tg measurements were performed by the same laboratory using the same method with an analytic sensitivity of 0.07 ng/ml and a functional sensitivity of 0.5 ng/ml.

RESULTS

Patient and tumor demographics and radioiodine therapy (Figures 1 to 4)

Patients were predominantly women with a median of 3 years from thyroidectomy to neck exploration for recurrent or residual disease. Of the 70 study patients, 22 (31%) were men and 48 (69%) were women. Median age at the time of PTC diagnosis was 35 years for men (range, 15 to 71) and 41 years for women (range, 18 to 73). Time from thyroidectomy to the first reexploration was a median of 3 years. Age was grouped as 40 years or younger in 10 of 22 men (46%) and in 38 of

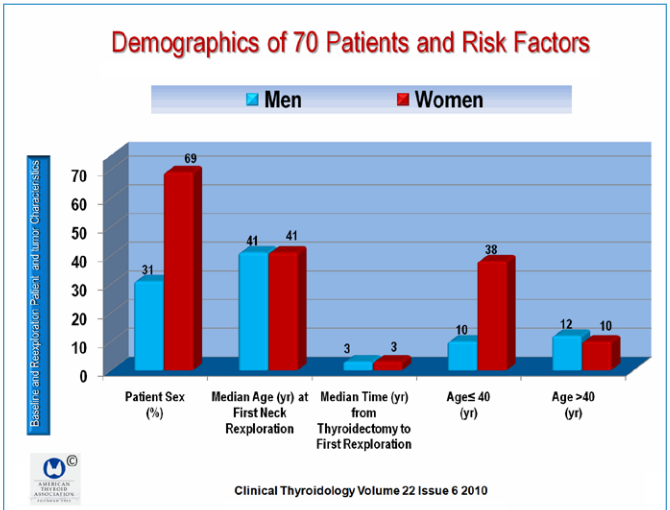


Figure 1. Figures 1 to 4 show the baseline patient and tumor demographics of 70 patients.

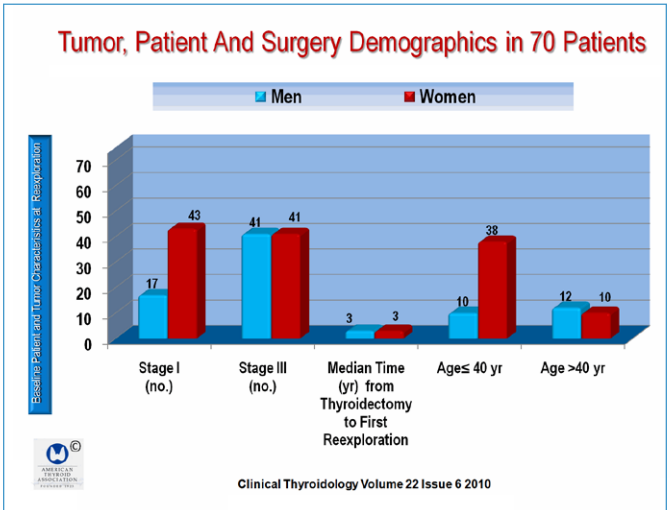
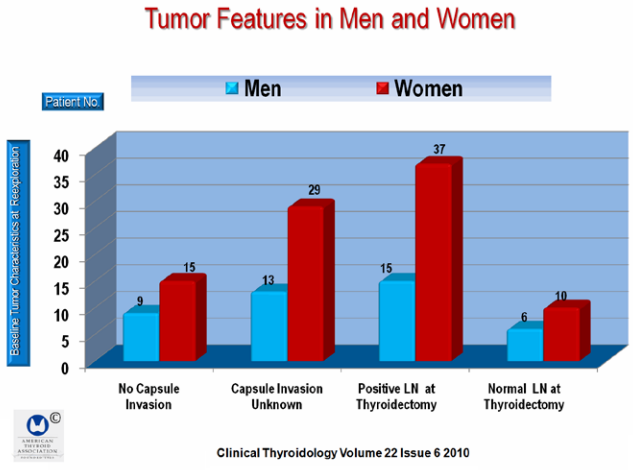


Figure 2. Figures 1 to 4 show the baseline patient and tumor demographics of 70 patients.



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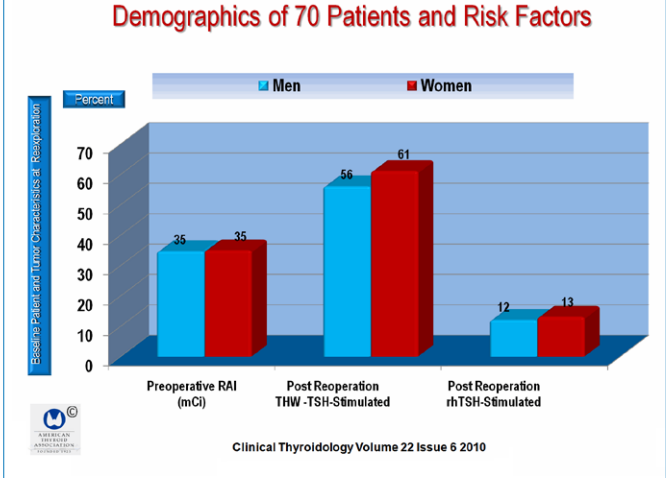

Figure 4. Figures 1 to 4 show the baseline patient and tumor demographics of 70 patients.

48 women (79%) and as 40 years or older in 12 of 22 men (55%) and in 10 of 48 women (20%) (Figure 1). The majority of patients had lymph-node metastases identified during the initial thyroid surgery, and the majority had tumor penetrating the thyroid capsule. All patients had at least one ^{131}I treatment and posttreatment whole-body scans. The patient and tumor features and radioiodine treatment are shown in Figures 1 to 4.

Surgical outcome (Figure 5)

A total of 107 lymphadenectomies were performed in 70 TgAb-negative patients between May 1999 and January 2010, 10 of which (9%) failed to identify recurrent PTC, which was based on US with FNAB (n = 7), palpation (n = 2), and 18FDG-PET (n = 1). Neck US with selective use of FNAB was performed in 102 of 107 patients (95%) before lymphadenectomy with FNAB performed in 48 of 102 patients (47%) that accurately identified recurrent PTC in 95 of 102 patients (93%).

Four of the seven patients with positive US findings had negative histology and a positive preoperative US-guided FNAB. One of the four had a preoperative Tg of 2.2 ng/ml during TSH suppression that decreased to <0.5 ng/ml postoperatively despite a negative surgical histology finding. Another of the four patients with positive preoperative US-guided FNAB cytology on two occasions had negative surgical findings; however, the lymph node was still present on postoperative neck US; in another patient, it was decided intraoperatively that the lesion could not be resected safely because of dense adhesions. Another patient with a positive US but no FNAB findings had positive surgical histology of the same target lesion at the third reoperation.

For all reoperations combined, neck US with selective use of FNAB accurately identified recurrent PTC in 100 of 102 lymphadenectomies (98%). The median number of lymph nodes removed was 11 (range, 1 to 61), with median positive PTC histology in 2 patients (range, 0 to 11). After the second reoperation, the median number of lymph nodes removed was 7 (0 to 55), with median positive histology in 2 patients (range, 0 to 12). After the third reoperation, the median number of lymph nodes removed was 3 (range, 1 to 34), with median positive histology in 2 (range, 1 to 5). The total number of lymph nodes removed, and the number of positive lymph nodes, was similar among the patients who achieved biochemical complete remission (BCR) as compared with the median number of lymph nodes dissected with pathology that did not identify recurrent PTC (range, 0 to 22) in four patients.

No patients had long-term hypoparathyroidism or recurrent laryngeal-nerve injury. One patient (1%) had a chyle leak during the second reoperation that was fixed with ligation of the thoracic duct but did not achieve BCR.

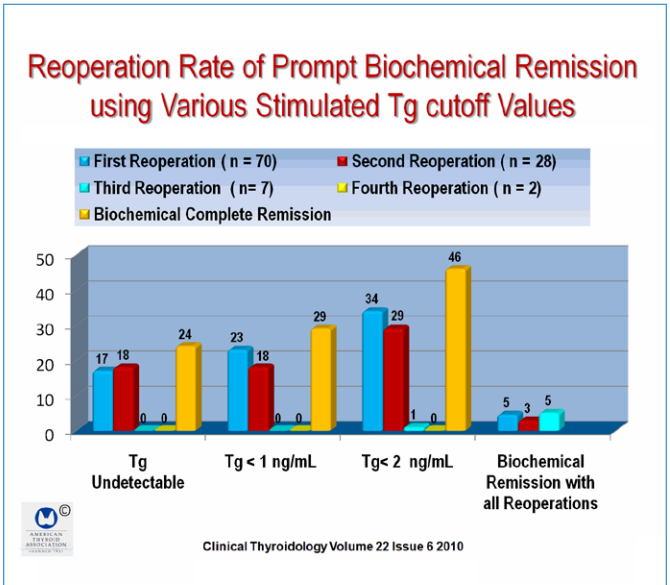

Figure 5. This figure shows the reoperation rate of prompt biochemical remission using various stimulated Tg cutoff values.

Biochemical complete remission

During long-term follow-up, two patients, both with stage I tumors, initially had detectable postoperative stimulated Tg of 0.5 and 1.2 ng/ml, respectively, after their first reoperations. Both achieved BCR, with repetitive TSH-stimulated Tg that persisted for 6.8 and 3.5 years, respectively, with negative neck US examinations being the only intervention, save for levothyroxine therapy, since reoperation. This delayed BCR was not included in the analysis of prompt postoperative BCR and may reflect the results of both surgery and late effects of the last radioiodine treatments 10.8 and 3.8 years before the BCR had occurred. However these two patients are included in the total of 19 of 70 patients (27%) who achieved BCR.

Prompt postoperative biochemical complete remission

Prior to the initial reoperation, mean basal Tg was 8.4 ng/ml (median, 4.0; range, undetectable to 100.5), and after this surgery, BCR occurred promptly in 12 of 70 patients (17%). The 12 who achieved BCR promptly had a mean basal Tg of 12.5 ng/ml (median, 4.2; range, undetectable to 200.5). Of the remaining 58 patients, 28 had a second reoperation, with prompt BCR in 5 (18%). Before the second reoperation, the mean basal Tg was 9.1 ng/ml (median, 1.3; range, undetectable to 99.1); however, the 5 who had prompt BCR had a median basal Tg that was undetectable (range, undetectable to 1.2 ng/ml).

Prior to the third reoperation, the mean basal Tg was 23.8 ng/ml (median, 4.5; range, undetectable to 116.0). Third reoperations were performed on seven patients, and none resulted in BCR. The mean and median basal Tg levels before the first reoperation in patients who experienced a prompt BCR with any reoperation was 9.7 and 2.7 ng/ml, respectively. In contrast, patients who failed to achieve BCR from that operation had significant reductions in unstimulated serum Tg levels after both the first operation (median decrease, 1.7 ng/ml; interquartile range, 0.3 to 7.4; P = 0.001) and the second reoperation Tg had a median decrease of 0.8 ng/ml; interquartile range, 0 to 6.2; P = 0.06).

In all, BCR was promptly achieved after 17 of 107 surgical procedures (16%), leading to prompt postoperative BCR in 17 of 70 patients (24%). Sixteen patients who achieved prompt BCR (94%) had stage I tumors; the remaining 20 patients all had stage III tumors.

Prompt BCR was achieved after the first reoperation in 5 of 15 patients (33%) when the preoperative Tg was detected only by stimulation, as compared with 7 of 55 (13%) in whom Tg was detected without stimulation (P = 0.11). In patients who had a second reoperation, prompt BCR was achieved in 3 of 8 (38%) when Tg was detected only with TSH stimulation, as compared with 2 of 20 (10%) when preoperative Tg was performed without stimulation (P = 0.12) (Figure 5).

For all patients after all surgical procedures, prompt BCR was achieved in 5 of 15 (33%) when preoperative Tg before the first reoperation was detected only by TSH stimulation, as compared with 12 of 55 (22%) in whom Tg before the first reoperation was detected without TSH stimulation (P = 0.05).

None of the following variables were significantly associated with BCR on univariate analysis: age at initial PTC diagnosis, sex, primary tumor capsular invasion, primary tumor size, lymph-node involvement, TNM stage at thyroidectomy, age at first reoperation, magnitude of the preoperative unstimulated Tg level, number of lymph nodes resected, one versus more than one resected metastatic lymph nodes at reoperation, number of lymph nodes containing PTC during lymphadenectomy, central versus lateral neck in more than one lymph-node compartment, and the number of lymph-node compartment reoperations.

LONG-TERM FOLLOW-UP

For patients achieving prompt postoperative BCR, overall, the mean follow-up was 60 months (range, 4 to 116), but no patient had evidence of biochemical or clinical recurrence. During long-term follow-up through January 2010, 10 of 53 the patients (19%), who did not achieve prompt BCR, were not tested for distant metastases, while the remaining 43 (81%) did achieve BCR and were evaluated by CT (in 36), chest radiograph (in 20), skeletal imaging with bone scan or MRI (in 5), whole-body 18FDG-PET (in 8), or Tg in the absence of TgAb (in 2).

After a median of 3.9 years, no distant metastases or deaths from thyroid cancer were identified from the first reoperation until the last test for distant metastases (range, 0.2 to 8.9 years). One patient treated with external-beam radiotherapy for FDG-avid cervical and upper mediastinal lymphadenopathy progressed even with four reoperations and sorafenib therapy.

CONCLUSION

Surgical resection of persistent cervical PTC lymph-node metastases may require several surgeries to achieve biochemical or clinical evidence of disease.

COMMENTARY

Lymph-node metastases from PTC are a common problem, routinely occurring in 5 to 10% of patients with PTC (1), reaching an incidence of 60% when routine lymph-node compartment dissection is performed (2). The risk for lymph-node metastases is generally greater in older patients and in those with some histologic subtypes, such as solid-variant PTC, the lymph-node treatment of which has not been fully elucidated. This multifaceted problem is related to the size and number of lymph-node metastases, their propensity to invade soft tissues, and the impact of oncogenes such as BRAF that portend a poor long-term outcome (3), to name a few (4;5). Whether radioiodine, surgical treatment, or both should be used to treat recurrent/persistent locoregional disease, thus, continues to be debated.

A stage-adapted approach to the treatment of regional lymph-node metastases is one method (6). Still, residual lymph-node metastases are relatively common after adjuvant ^{131}I therapy with serum Tg levels that remain detectable, especially in high-risk patients who have tumors with little or no ^{131}I uptake (6). Most experts agree that routine (i.e., prophylactic) lymph-node dissection is unnecessary for low-risk well-differentiated thyroid cancer. Because lymph-node metastases are often occult, surgery of cervical lymph-node compartments may be associated with a more than usual risk for surgical complications (7). It is especially important to note the size of lymph nodes, as the outcome of macrometastases is prognostically much more serious as compared with that for micrometastases that have a low rate of recurrence and a generally good prognosis (8).

This study by Osama et al. provides important information concerning the outcome of lymphadenectomy in 58 patients with cervical recurrent/persistent PTC. Biochemically complete remission was achieved in 12 patients (17%), using the most stringent definition for no evidence of disease, which is that of the European Thyroid Association (9) and American Thyroid Association (10); they recommend the following criteria for no evidence of disease: (1) no clinical evidence of tumor, (2) no imaging evidence of tumor (no uptake outside the thyroid bed on the initial posttreatment whole-body scan, or, if uptake outside the thyroid bed had been present, no imaging evidence of tumor on a recent diagnostic scan and neck US), and (3) undetectable serum Tg levels during TSH suppression and stimulation in the absence of interfering antibodies.

After a mean follow-up of 60 months (range, 4 to 116), no patient had a relapse. Still, patients who did not achieve a remission had a reduction in serum Tg after the first and second operations ($P<0.001$ and $P = 0.008$, respectively). Moreover, no patient had distant metastases or died of disease. Among the patients who did not experience a remission, Tg levels were significantly reduced, and the authors acknowledge that further follow-up will be necessary for this group of patients.

Lastly, the multiple surgeries were performed without long-term hypoparathyroidism or recurrent laryngeal-nerve injury. One patient had a chyle leak during the second reoperation that was fixed with ligation of the thoracic duct.

This study shows the significance of ongoing surveillance and the careful selection of patients for repeated surgery without repeating ^{131}I therapy. The validation Retreating patients with persistent lymph-node metastases may rest on a unique study by Links et al. (11), in which survival rates were transformed into standardized survival time to adjust for the baseline mortality rate in the general population. The outcome of the study was that disease-free patients had a normal residual life span, whereas life expectancy was reduced to 60% in patients with persistent disease. This suggests that residual disease should not be treated lightly.

— Ernest L. Mazzaferri, MD, MACP

References

1. Mazzaferri EL, Kloos RT. Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 2001;86:1447-63.

2. Wada N, Duh QY, Sugino K, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. Ann Surg 2003;237:399-407.

3. Xing M. BRAF mutation in papillary thyroid cancer: pathogenic role, molecular bases, and clinical implications. Endocr Rev 2007;28:742-62.

4. Rodolico V, Cabibi D, Pizzolanti G, et al. BRAF V600E mutation and p27 kip1 expression in papillary carcinomas of the thyroid <or=1 cm and their paired lymph node metastases. Cancer 2007;110:1218-26.

5. Leboulleux S, Rubino C, Baudin E, et al. Prognostic factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph node metastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. J Clin Endocrinol Metab 2005;90:5723-9.

6. Hamming JF, van de Velde CJ, Fleuren GJ, et al. Differentiated thyroid cancer: a stage adapted approach to the treatment of regional lymph node metastases. Eur J Cancer Clin Oncol 1988;24:325-30.

7. Dralle H, Machens A. Surgical approaches in thyroid cancer and lymph-node metastases. Best Pract Res Clin Endocrinol Metab 2008;22:971-87.

8. Cranshaw IM, Carnaille B. Micrometastases in thyroid cancer: an important finding? Surg Oncol 2008;17:253-8.

9. Pacini F, Schlumberger M, Dralle H, et al. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006;154:787-803.

10. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.

11. Links TP, Van Tol KM, Jager PL, et al. Life expectancy in differentiated thyroid cancer: a novel approach to survival analysis. Endocr Relat Cancer 2005;12:273-80.