Patients with very low-risk papillary thyroid microcarcinoma treated with total or near-total thyroidectomy rarely have persistent or recurrent disease and likely do not require adjuvant radioiodine therapy

Durante C, Attard M, Torlontano M, Ronga G, Monzani F, Costante G, Ferdeghini M, Tumino S, Meringolo D, Bruno R, De Toma G, Crocetti U, Montesano T, Dardano A, Lamartina L, Maniglia A, Giacomelli L, Filetti S. Identification and optimal postsurgical follow-up of patients with very low-risk papillary thyroid microcarcinomas. J Clin Endocrinol Metab 2010.doi:10.1210/jc.2010-0762

SUMMARY

BACKGROUND

For the past three decades, the incidence of thyroid cancer has been steadily rising worldwide and the vast majority of it (80%) is papillary thyroid cancer. Approximately half of these tumors are 10 mm or less and are designated as papillary thyroid microcarcinoma (PTMC). Despite the small size of these tumors (≤1 cm), there has been considerable controversy concerning their management. This is a retrospective study that tests the hypothesis that clinical criteria could be used to identify patients with the lowest risk for PTMC mortality and recurrence. This retrospective study is based on explicit criteria aimed at tailoring a postoperative management protocol for patients with very-low-risk PTMC that would diminish the odds of developing recurrent or progressive disease.

SUBJECTS AND METHODS

Data for this study were collected from nine hospital-based referral centers for thyroid disease in Italy, including seven thyroid clinics and two nuclear medicine units that identified a total of 946 patients with PTMC treated over the past two decades. Study coordinators in each center identified 710 consecutive patients (75%) with sufficient data to satisfy the criteria for very-low-risk PTMC, which included all of the following: no family history of thyroid cancer, no history of head and neck irradiation, tumor stage pT1, tumor size ≤1 cm, pN0 and pM0, with no extension beyond the thyroid capsule, unifocal tumors, and tumors without histologically aggressive subtypes, such as tall-cell PTMC.

The study subjects comprised 312 patients with complete follow-up from the time of surgical diagnosis through at least 5 years of follow-up or until the date of death. An electronic form was completed that provided all the information required to fulfill the study criteria for very-low-risk PTMC, surgical treatment and radioiodine ablation, levothyroxine therapy and follow-up findings including the cervical ultrasound findings, and laboratory results at the last follow-up visit.

All patients had total or near-total thyroidectomy, and the histologic surgical specimens were cut into fine microscopic specimens for examination to exclude other tumor foci. Radioiodine ablation was performed at the discretion of the team treating the patient, which reflected the institutional guidelines at the time the patient had surgery. Levothyroxine was administered to maintain serum thyrotropin (TSH) levels at normal or suppressed levels. All patients had follow-up according to the same protocol. They had initial postoperative follow-up within 12 months after surgery and yearly visits thereafter, at which time a physical examination was performed and serum TSH, thyroglobulin (Tg), and Tg autoantibody (TgAb) levels were measured. However the mainstay of follow-up was neck ultrasonography with Doppler scanners, which was the most sensitive technique for detecting locally recurrent tumor. The standard ultrasound criteria were used to identify cervical-lymph-node metastases, and fine-needle aspiration biopsy was performed for suspicious lymph nodes, and Tg levels were measured in the needle washout fluid. After 1997, aspirates were also assayed for Tg, TSH, and mRNA. At each follow-up visit, the outcome was classified as positive or negative for persistent or recurrent disease on the basis of ultrasound findings and unstimulated serum Tg levels. In the presence of negative ultrasound findings in a patient who had ^{131}I remnant ablation, serum Tg levels were considered suspicious if they were within the detectable range of the assay used. If ^{131}I ablation had not been performed, serum Tg was considered suspicious if the Tg levels increased over time.

RESULTS

Characteristics of the Study Population (Figure 1)

The characteristics of the study population are summarized in Figure 1. In all, 239 of 312 (77%) of the PTMCs had been diagnosed after surgery for multinodular goiter. The other 73 had PTMC diagnosed preoperatively with fine-needle aspiration

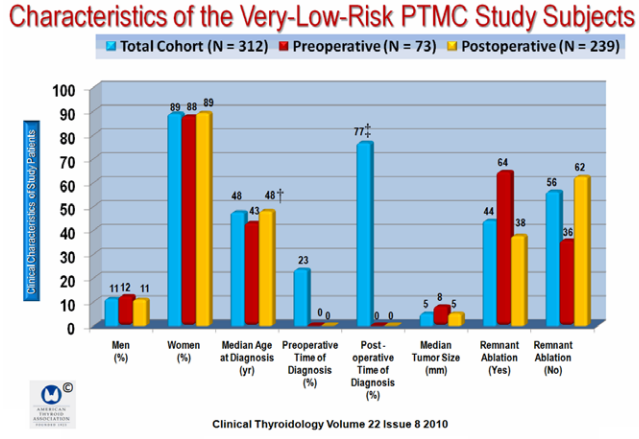

Figure 1. This figure shows the characteristics of the total study cohort and the number of patients that had a diagnosis of PTMC made preoperatively or postoperatively. Patients at the time of diagnosis were significantly older than the patients whose diagnosis of PTC was made after surgery for multinodular goiter. †P = 0.003 comparing preoperative or postoperative age of diagnosis. ‡P< 0.001 for tumor size and comparing those with and without remnant ablation. The data in Figure 1 are derived from Table 2 in the study by Durante et al.

biopsy, which tended to be performed in younger patients with larger tumors than those diagnosed postoperatively. Also, the younger patients were more likely to have ^{131}I remnant ablation, which was performed in 137 patients (44%) of the total cohort. A median of 73 mCi of ^{131}I was administered. In all patients, the whole-body posttherapy ^{131}I scan revealed ^{131}I uptake exclusively in the thyroid bed.

Follow-up and Clinical Outcome in the Study Population (Figure 2)

Figure 2 summarizes the findings at the end of the study for the total cohort, and subgroups are defined on the basis of time of diagnosis and treatment with ^{131}I.There were no significant differences in the time of diagnosis, although follow-ups were significantly longer in the group that had received ^{131}I remnant ablation.

None of the patients died of thyroid cancer or had to have more surgery. The first follow-up cervical ultrasound after surgery at 6 to 12 months after surgery found no evidence of lymph-node metastases in any of the 312 patients and was consistently confirmed in all patients by the results of subsequent annual follow-up and final ultrasound examinations. The negative predictive value of the initial ultrasound study was thus 100%.

Thyroglobulin Levels at the End of the Follow-up Period (Figure 3)

Serum Tg levels were not correlated with serum TSH levels in both the ^{131}I and non-^{131}I subgroups. All 137 patients treated with ^{131}I remnant ablation had undetectable serum Tg levels, which confirmed the disease-free status of the patients indicated by the ultrasound findings. The final Tg levels were also <1 ng/ml in most of the patients (163 of 157; 93%) who had not had ^{131}I remnant ablation. The characteristics of the other 12 patients in this group are shown in Figure 3. Their final serum Tg levels ranged from 1.3 to 6.0 ng/ml. In all 12 patients, the Tg levels had remained stable or decreased progressively during follow-up. Although thyroid remnants were documented by cervical ultrasonography, none of the final scans showed any sign of lymph-node metastases. Patient 12, whose final Tg was especially high at 6.0 ng/ml, was extensively investigated to rule out persistent or recurrent disease; after the administration of recombinant human TSH (rhTSH), his Tg increased to 10 ng/ml and the whole-body scan revealed uptake only in the thyroid bed, which the authors concluded were very unlikely to be expressions of persistent disease.

Patients with Detectable Tg Levels at the Last Follow-up Visit

Twelve patients had detectable serum Tg levels at the last follow-up visit. All were women, and the time of diagnosis was postsurgical in 10 patients and presurgical in 2; median age at the time of diagnosis was 50±9.4 years (range, 34 to 64). The mean final Tg was 2.8±1.3 ng/ml (range, 1.3 to 3.97). The mean final TSH was 1.06±1.45 mIU/L (range, 0.03 to 5.1) and the mean follow-up 10.2±5.5 years (range, 5.9 to 20.4). (These data are calculated from Table 4). None of these patients had evidence of persistent or recurrent disease

CONCLUSION

Very-low-risk patients with PTMC had persistently negative neck ultrasound examinations, even in the 66 patients (24.3%) that had follow-up for more than 10 years, which thus indicates that in the vast majority of patients (~75%), effective postoperative surveillance can be based exclusively on neck ultrasonography. The initial postoperative studies found a negative predictive value of 100% for persistent or recurrent disease after surgery for up to 23 years, suggesting that yearly neck ultrasound examinations are unnecessary, at least after 5 years of follow-up, when the most recurrences are found. Also, the use of adjuvant ^{131}I remnant ablation in this group of patients, especially to monitor serum Tg levels is not likely to provide additional benefit to the patient, as shown in the group that did not have ^{131}I remnant ablation.

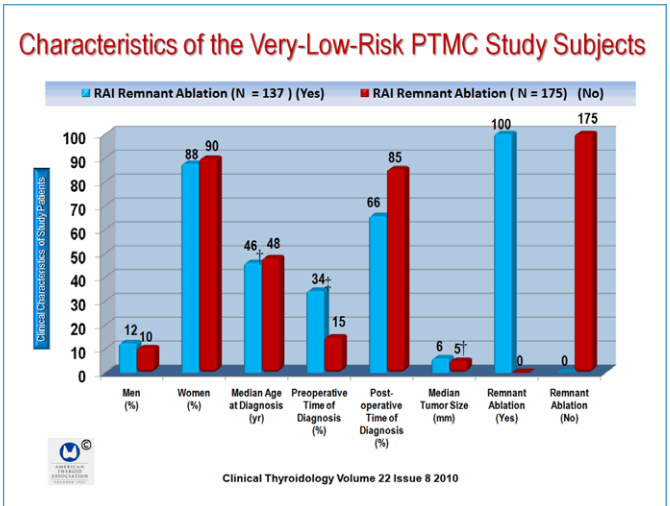

Figure 2. This figure shows the characteristics of patients who had remnant ^{131}I ablation and those who did not have remnant ablation. Those who had remnant ablation were significantly younger (46 years) as compared with those who did not have ^{131}I ablation (48 years) †P = 0.041, and the time of diagnosis was significantly different (43 vs. 47.5 hrs ‡P< 0.0001. The rest of the differences in this figure are not statistically significant. RAI = radioactive iodine. The data in Figure 2 are derived from Tables 2 and 3 in the study by Durante et al.

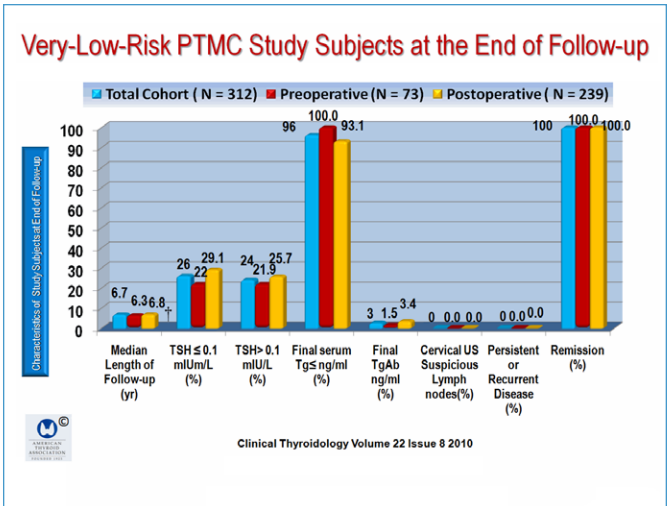

Figure 3. This figure shows the characteristics of the very-low-risk PTMC study population at the end of the follow-up period. The length of follow-up was greater in patients who had remnant ablation than in those who did not (median years of 6.3 vs 6.8). †P = 0.028. The rest of the differences were not statistically significant, except for the final serum Tg level, which was 72 ng/ml in the preoperative group and 229 in the postoperative group; ‡P< 0.001). US = ultrasound; TgAb = antithyroglobulin antibodies

COMMENTARY

The increasing incidence of thyroid cancer In the United States and other countries is thought by some to be predominantly due to the increased detection of small papillary cancers that require little or no therapy (1). This alone is a controversial opinion based upon data in the Surveillance, Epidemiology, and End Results (SEER) database (2).

Thyroid microcarcinoma, defined as a tumor ≤1 cm, is thus generally regarded as a low-risk tumor that requires minimal or no therapy. The ATA guidelines (3) recommend that thyroid lobectomy alone may be sufficient treatment for small (<1 cm), low-risk, unifocal, intrathyroidal papillary carcinomas in the absence of prior head and neck irradiation or radiologically or clinically involved cervical-lymph-node metastases. (Recommendation rating: A)

Still, there is considerable controversy concerning the management of these small tumors (4). Part of the disagreement is that large studies have found that there is a risk for tumor recurrence and cancer-specific mortality for tumors <1 cm. A study of 52,173 patients by Bilimoria et al. (5) found that the 10-year tumor recurrence rate of papillary cancers <1 cm was 4.6% and the 10-year cancer-specific mortality 2%.

A study of by Noguchi et.al(6) of 2070 patients with PTMC found that over a 35-year follow-up, there were 73 cases of recurrence from the time of initial surgery to the first recurrence, among which there were distant metastases outside the neck, 1 in the lung, 4 in the bone, and 1 with multiple distant metastases. In the interval between the primary surgery and the second recurrence there were 12 cases of recurrence, including 4 in lung, 1 in bone and 1 in the mediastinum. The Bilimoria and Noguchi studies thus show a spectrum of clinical behavior of PTMC (7;8).

The very important study by Durante et al. directly addresses the conflicting views concerning the initial management of PTMC by carefully defining a very-low-risk group of tumors. This large multicenter study of 710 patients defined very-low-risk PTMC on the basis of clinical features that affected outcome, including all of the following: unifocal tumor, total or near-total thyroidectomy, no family history of thyroid cancer, no history of head and neck irradiation, tumor stage pT1, ≤1 cm, pN0 and pM0 and no extension of tumor beyond the thyroid capsule. The authors documented that this subset of tumors is indeed very-low-risk and that they require little therapy other than total or near-total thyroidectomy. After a mean follow-up of 10.2±5.5 years (range, 5.9 to 20.4), none of these patients had evidence of persistent or recurrent disease over an extended follow-up. This is the main feature of the study.

I think this is a major contribution that carefully identifies a group of patients with very-low-risk PTMC that require only total or near-total thyroidectomy without remnant ablation and TSH suppression.

The Durante study has a second feature: it will focus the debate on the remaining group of patients with PTMC who do not have the defining characteristics for very-low-risk tumors identified by Durante et al.

For example, an important study by Bonnet et al. (9), in which total or near-total thyroidectomy with prophylactic, multi-compartment neck dissection was performed shows that patients with tumors <1 cm to 2 cm still are at risk for recurrence unless the residual lymph-node metastases, invasive tumors, or tumors with aggressive histology are treated with remnant ablation.

Taken together, these two studies shine a bright light on the ongoing debate concerning the management of PTMC that offers several therapeutic options to patients with different PTMC tumor characteristics.

— Ernest L. Mazzaferri, MD, MACP

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