Patients with papillary thyroid microcarcinoma may have a reduced risk for recurrence when treated with total or near-total thyroidectomy

Ross DS, Litofsky D, Ain KB, Bigos T, Brierley JD, Cooper DS, Haugen BR, Jonklaas J, Ladenson PW, Magner J, Robbins J, Skarulis MC, Steward DL, Maxon HR, Sherman SI. Recurrence after treatment of micropapillary thyroid cancer. Thyroid 2009;19:1043-8.

SUMMARY

BACKGROUND The initial treatment of papillary thyroid microcarcinoma (PTMC) is controversial, mainly because of the low mortality and recurrence rates of tumors ≤1 cm. There is even controversy concerning the definition of PTMC. The World Health Organization describes PTMC as a tumor ≤1 cm in diameter that is found incidentally, whereas the TNM (tumor–node–metastases) system simply classifies PTMC as a tumor ≤1 cm. The main clinical problem with these tumors is recurrence, which may be found years after the initial tumor has been treated. This is a study by the National Thyroid Cancer Treatment Cooperative Study Group. The aim of the study was to analyze recurrence in a set of patients with PTMC with or without multifocal tumor or lymph-node metastases.

METHODS This is a retrospective study of a group of nonrandomized patients who were enrolled in the National Thyroid Cancer Treatment Cooperative Study Group, which established a tumor registry in 1987 and has subsequently obtained follow-up data on this group of patients. Approximately 4830 patients were registered from January 1987 through July 2006. Treatment was solely at the discretion of the attending physicians. Initial therapy was surgery, with or without ^{131}I administration, within 6 months after the time of surgery. There were no uniform protocols for initial therapy and follow-up among the 11 North American centers contributing to the registry. At entry, disease stage was classified by the individual clinicians at each center using a previously described staging system. Patient status was based on imaging studies and serum thyroglobulin (Tg) measurement as: (1) no residual disease, (2) biochemical evidence of disease only, or (3) residual disease with documentation of the disease sites. In the present study, death was not considered to be an event for analysis of recurrence-free survival.

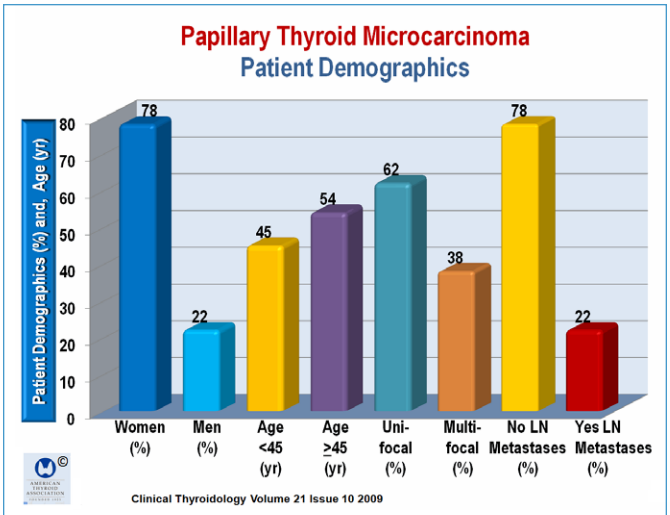

Figure 1. This figure shows the demographics of patients with thyroid microcarcinoma and the features of the tumors. LN = lymph-node metastases.

RESULTS

Demographics of the Study Group (Figures 1 to 3)

A total of 3923 of the 4830 study patients had papillary thyroid cancer (81%), including all variants of the tumor. Of the 3923 patients, 710 (18%) had PTMC. Excluded from the study were 12 patients with missing data, 27 with gross extrathyroidal invasion of tumor, 9 with distant metastases and another with both gross extrathyroidal invasion and distant metastases. Here and elsewhere percentages are rounded to an integer. The final study group thus comprised 611 patients with intrathyroidal PTMC, all of whom were considered to be free of disease at the time of the

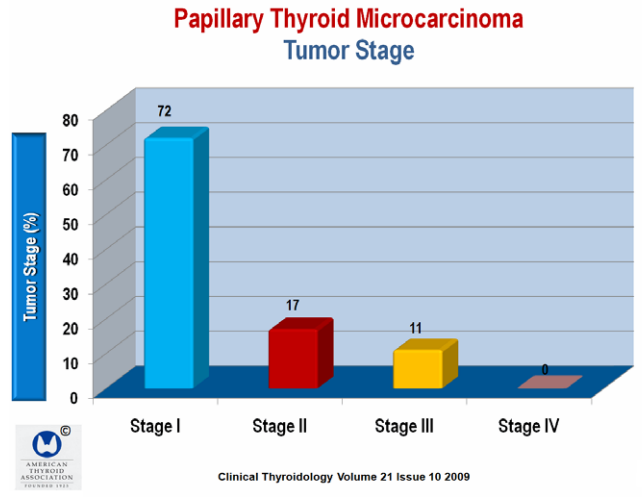

Figure 2. This figure shows the tumor stage as described by the authors of this study.

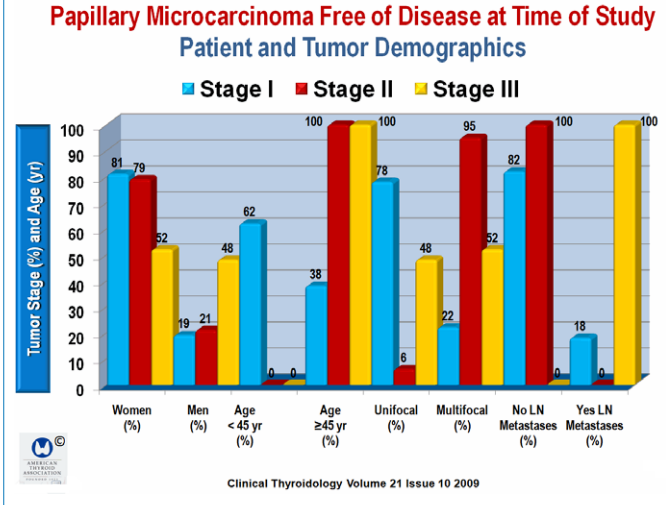

Figure 3. This figure shows the patient demographics according to tumor stage. LN = lymph-node.

study. Of the 611 patients, 477 were women (78%) and 133 were men (22%); the mean age was <45 years in 276 patients (45%) and ≥45 years in 332 (54%). PTMC was unifocal in 381 patients (62%) and multifocal in 230 (38%). Lymph-node metastases were present in 135 patients (22%) and absent in 476 (78%) (Figure 1). Tumor was stage I in 72% of patients, stage II in 17%, and stage III in 11% (Figure 2). The age, sex, extent of unifocal and multifocal tumors, and lymph-node metastases are shown in Figure 3.

Tumor Recurrence (Figure 4)

After a mean follow-up of 4 years (median, 3), 38 patients (6%) had tumor recurrence. The overall mean (±SD) time to recurrence was 2.8±2.4 years (range, 0.5 to 10.9). Patients who were treated with ^{131}I had a shorter time to recurrence (2.3±2.2 years). The sites of recurrence were known in 34 of 38 patients (89%). Recurrences were found in the thyroid bed in 17 (2.8%) patients ,in regional lymph nodes with or without thyroid bed recurrences in 14 (2.3%), in mediastinal lymph nodes in 2 (0.3%), and in distant sites in 1 (0.2%) and were not recorded in 4 (0.6%.) There was no significant difference in recurrence rates among patients with unifocal and multifocal tumors.

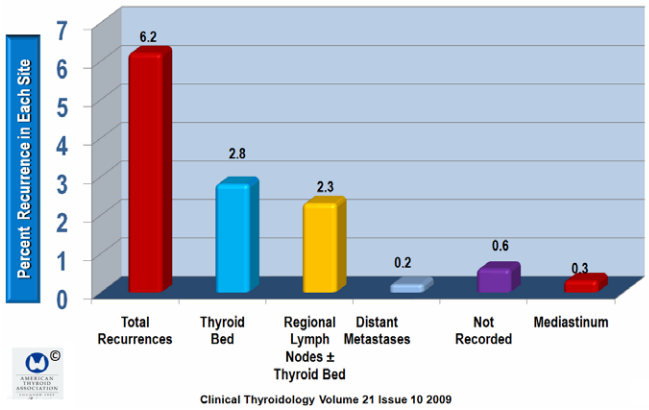

Figure 4. This figure shows the sites of tumor recurrence for microcarcinomas.

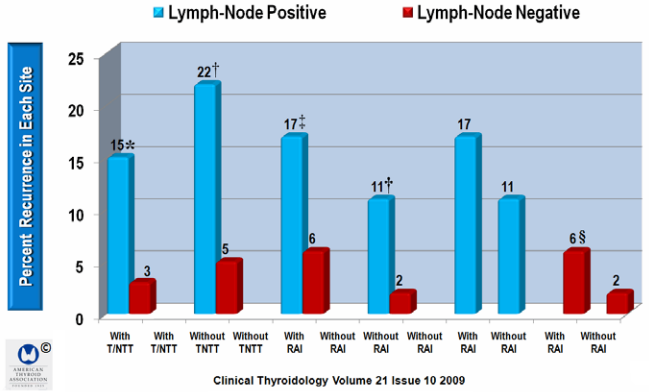

Figure 5. This figure shows some of the effects of ^{131}I therapy and surgical treatment of microcarcinomas in patients with and those without lymph-node metastases. *P<0.0001, †P, 0.003, ‡P<0.006, §P = 0.05, all comparing node-positive patients with node-negative patients.

The Effects of ^{131}I Therapy and the Extent of Surgery on Outcome (Figures 5 and 6)

A series of univariate analyses are shown in Figures 5 and 6. Patients with lymph-node metastases had higher recurrence rates as compared with patients without lymph-node metastases whether they were treated with total or near-total thyroidectomy (15% vs. 3%; P<0.001) or ^{131}I (22% vs. 5%; P = 0.003). Among patients who did not have nodal metastases, ^{131}I therapy was associated with an increased rate of recurrence, although the difference was not statistically significant.

Patients with multifocal tumors treated with less than near-total thyroidectomy had higher recurrence rates than those with unifocal tumors (18% vs. 4%; P<0.01). Although recurrence rates were lower in patients with unifocal or multifocal tumors treated with total or near-total thyroidectomy as compared with less than near-total thyroidectomy (6% vs. 18%), the difference was not statistically significant (P= 0.06). There was no statistical difference in recurrence rates in patients with multifocal tumors who were treated with ^{131}I as compared with patients who were not treated with ^{131}I.

Among patients not treated with ^{131}I, the recurrence rates were higher in patients with multifocal tumors (7%) as compared with patients with unifocal tumors (2%; P<0.02). Still, there were no statistically significant differences whether or not patients were treated with ^{131}I.

CONCLUSION Patients with multifocal tumors treated with less than near-total thyroidectomy may have higher recurrence rates than those with unifocal tumors. Although recurrence rates are lower in patients with unifocal or multifocal tumors treated with total or near-total thyroidectomy, the difference is not statistically significant.

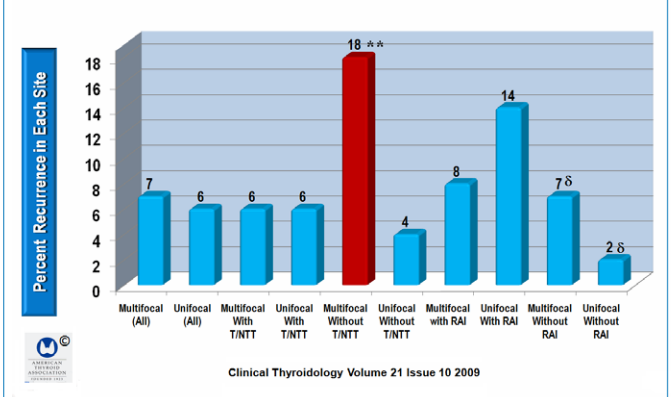

Figure 6. This figure shows some of the univariate analyses among various combinations of therapy. **P = 0.01, comparing unifocal and multifocal tumors with and without ^{131}I. δP = 0.02, comparing multifocal tumors without ^{131}I and unifocal tumors without ^{131}I therapy. T/NTT = total/near-total thyroidectomy; RAI = ^{131}I therapy.

COMMENTARY

This interesting study was designed to analyze recurrence rates in patients with multifocal PTMCs and to assess the efficacy of therapy. The study comprised 611 patients with a mean follow-up of 4 years (median 3). Perhaps the most important finding was that patients with PTMC associated with lymph-node metastases had more recurrences than did patients without them, regardless of the extent of surgery or the use of radioiodine. Moreover, the study found that overall recurrence rates did not differ between unifocal and multifocal tumors. Still, patients with multifocal tumors treated with less than near-total thyroidectomy had significantly higher recurrence rates than did patients with unifocal tumors. Although patients with multifocal tumors treated with total or near-total thyroidectomy had fewer recurrences than did patients with unifocal tumors, the differences were marginal and not statistically significant. These findings are at odds with several large studies.

At odds with the findings by Ross et al. is a study by Bilimoria et al. (1) that is arguably the most authoritative analysis on outcome following surgical therapy for papillary thyroid cancer, which analyzed 52,163 patients with papillary thyroid cancer. Of this group, 12,469 patients had PTMC (24%). Total thyroidectomy was performed in 8775 patients (20%), and lobectomy was performed in 3686 (42%) with PTMC. For PTMC <1 cm, the extent of surgery did not impact recurrence or survival, whereas for tumors ≥1 cm, lobectomy resulted in a higher risk of recurrence and death. The study found a 10-year recurrence rate of 5% and a 10-year mortality rate of 2% for patients with PTMC. Largely on the basis of this study, the ATA guidelines suggest lobectomy for PTMCs.

A study by Chow et al. (2) of 203 patients with PTMC found after a follow-up of 8.4 years that multifocal tumor was correlated with lymph-node metastases at the time of presentation. When lymph-node metastases and multifocal disease were present at the time of diagnosis, ^{131}I ablation reduced the lymph-node recurrence rate to 0.27 (P = 0.04). Moreover, in the presence of lymph-node metastases, the rate of distant metastases increased 11.2-fold (P = 0.03). Despite the overall excellent prognosis for patients with PTMC, the authors reported a 1% disease-related rate of mortality and a 5% rate of lymph-node recurrence. Multivariate analysis found no statistically significant difference in outcome between total or near-total thyroidectomy as compared with outcome in patients treated with thyroid lobectomy.

A study by Baudin et al. (3) of 281 patients with PTMC found after a median follow-up of 7.3 years that multifocal tumors had a 20% recurrence rate, as compared with only 2 recurrences(3%) among 60 patients with unifocal PTMC. Multivariate analysis showed two parameters significantly influenced the outcome of PTMC recurrence: the number of histologic foci (P<0.002) and the extent of initial thyroid surgery (P<0.01). The authors concluded that the recurrence rate for PTMC appears to be low (4%) and that lobectomy is the treatment of choice for patients with TMC when only one tumor focus is found, and total thyroidectomy is the optimal treatment for patients with multiple tumor foci.

Ross et al. indicate that their study has are several significant limitations, including the small number of patients. Because of the small number of study subjects, they were unable to analyze groups based on age, and differences among groups were not significant in multivariate analysis. The latter is particularly important, given the several univariate analyses that showed significant differences. The fact that a multivariate analysis found no variables of significance leaves uncertainty about which of the findings represent independent variables that influence outcome.

For now —and based upon the studies of Bilimoria, Chow and Baudin—the most reliable recommendation for therapy for papillary thyroid microcarcinomas seems to be that lobectomy is a the best option for unifocal tumors and total thyroidectomy is best for multifocal tumors, and small amounts of ^{131}I in the range of 30 mCi should be considered when lymph-node metastases are present.

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References

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