Lymph-node metastases and TNM stage portend unfavorable prognosis in patients with well-differentiated thyroid microcarcinoma of various histologies

Tzvetov G, Hirsch D, Shraga-Slutzky I, Weinstein R, Manistersky Y, Kalmanovich R, Lapidot M, Grozinsky-Glasberg S, Singer J, Sulkes J, Shimon I, Benbassat C. Well-differentiated thyroid carcinoma: comparison of microscopic and macroscopic disease. Thyroid 2009;19:487-94.

SUMMARY

BACKGROUND The incidence of thyroid cancer has been gradually increasing over the past three decades, especially that of papillary thyroid cancers ranging in size from <1 to 2 cm. As a consequence, this has produced a diverse range of opinions concerning the management of this low-risk group of cancers. This is a retrospective study that compares the outcomes of well-differentiated microscopic and macroscopic nonmedullary thyroid cancers of follicular-cell origin.

METHODS This is a retrospective study of patients treated for thyroid cancer in the Rabin Medical Center in Israel from 1973 through 2005, when a thyroid cancer tumor registry was established. The study subjects comprised 768 of 1030 patients (75%) with well-differentiated thyroid cancer (DTC) for whom the registry data were complete (Here and elsewhere, percentages >1% are rounded to the integer.) Of the 768 patients with DTC, 543 had macroscopic tumors (71%) and 225 had microscopic tumors (29%). The remaining patients were excluded from this study because of incomplete data. Microscopic DTC was defined as a tumor ≤1 cm, regardless of the circumstances in which the tumor was identified, and as macroscopic if the tumor was >1 cm. Most patients were treated with total thyroidectomy, although 10 with microscopic tumors (1%) and 13 with macroscopic tumors (2%) were included in the total thyroidectomy group. Lymph-node metastases were treated with neck dissection, the extent of which was not further defined. Follow-up studies were performed with serum thyroglobulin (Tg), neck ultrasonography, and diagnostic whole-body radioactive iodine (^{131}I) scans (DxWBS), which were performed either periodically or on an as-needed basis.

The tumor registry established in 2005 provided data on patient age, sex, tumor histopathology, and primary therapy and the extent of tumor, local recurrence, and distant metastases. In some cases, however, the original diagnoses dated back as far as 1970 and were not available for review. Tumor was regarded as intrathyroidal if vascular invasion or tumor extension remained within the thyroid margins. Tumor multifocality was defined as

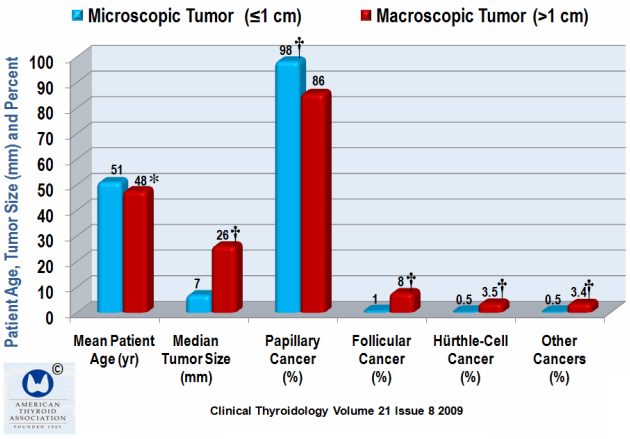

Figure 2. This figure shows mean patient age, median tumor size, and tumor histology. *P<0.01 and †P <0.001, comparing microscopic and macroscopic tumors. Derived from data in Table 1 of Tzvetov et al.

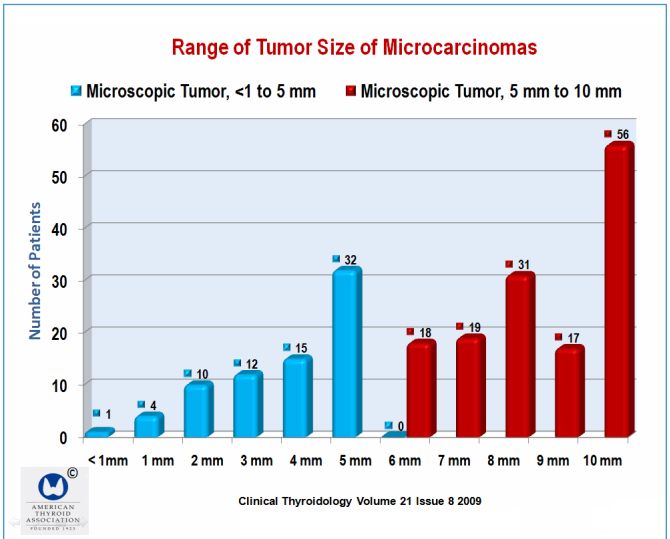

Figure 1. This figure shows the range of microcarcinomas in this study. Adapted from Figure 1 in Tzvetov et al.

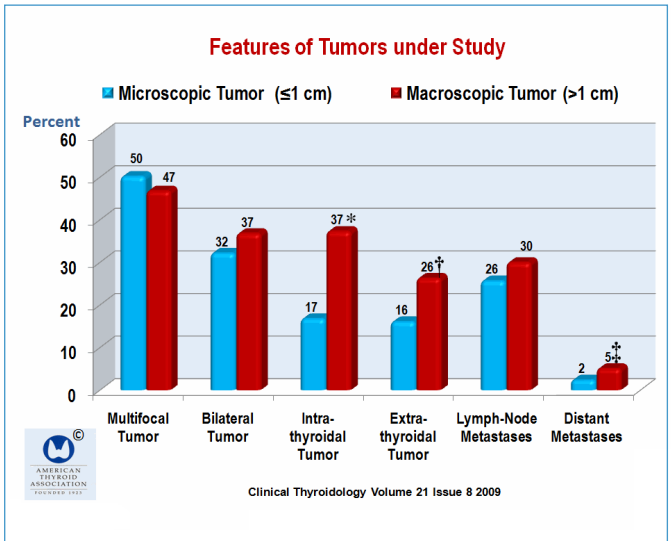

Figure 3. This figure shows the features of the tumors in this study. *P<0.01. †P = 0.02. ‡P = 0.16. Derived from Table 1 in Tzvetov et al.

more than one tumor in one or both thyroid lobes. Persistent or recurrent disease was defined as detectable tumor 1 year after initial therapy, which included surgery with or without ^{131}I therapy. Tumor was identified by neck ultrasonography, cytologic findings, elevated serum Tg levels, or ^{131}I uptake outside the thyroid bed. Persistent or recurrent tumors were grouped together as recurrent disease. Patients were considered free of disease if they had undetectable TSH-stimulated serum Tg levels, negative neck ultrasonography and a negative DxWBS at the last follow-up study. Staging was performed according to the 6th edition of the TNM (tumor–node–metastasis) staging system.

RESULTS Of the patients with DTC, 225 (29%) had microscopic and 543 (71%) had macroscopic tumors. The range of microscopic tumor size is shown in Figure 1. Hemithyroidectomy was performed in 12 patients (2%) versus 52 patients (23%), in the microscopic and macroscopic groups, and neck dissection was performed in 43 (19%) versus 98 (18%) (P not significant [NS]). The median ^{131}I activity that was administered initially was 100 mCi (range, 30 to 250) versus 150 mCi (range, 30 to 250).

At the time of initial treatment, the mean (±SD) patient age was 51±14 versus 47.5±16.1 years (P<0.01) and the mean tumor size was 6.8±2.7 versus 25.9±13.5 mm for patients with microscopic and macroscopic tumor. Of the microscopic cancers, 221 were papillary (98%), 2 were follicular (0.9%), 1 was a Hürthle-cell cancer (0.05%), and 1 was reported as "other cancer" (3.4%). Of patients with macroscopic tumors, 464 of 543 (86%) had papillary, 41 follicular (8%), 19 Hürthle-cell (4%), and 18 (3%) other cancer (P<0.001 for microscopic vs. macroscopic tumors for each of the 4 histologic types reported) (Figure 2). Multifocal tumor was found in 108 (50%) versus 241 (47%) patients, with microscopic and macroscopic tumor (P = NS); bilateral tumor was found in 69 (32%) versus 187 (37%) (P = NS). Intrathyroidal tumor was found in 35 (17%) versus 176 (37%) of the microscopic and macroscopic tumors (P<0.001), extrathyroidal extension in 36 (16%) vs. 131 (26%) (P = 0.02), lymph-node metastases in 55 (26%) versus 154 (30%) (P = NS), and distant metastases in 5 of 208 (2%) versus 26 of 508 (5%) (P = 0.016) (Figure 3). The TNM stage was I in 139 (74%) versus 269 patients (63%) (P = 0.04), stage II in 1 (0.5%) versus 51 patients (12%) (P = 0.02), stage III in 33 (18%) versus 59 (14%) (P = NS), and stage IV in 15 (8%) versus 45 (11%), with microscopic and macroscopic tumors (P = NS) (Figure 4).

The median duration of follow-up was 5 years in both groups. Tumor recurrence was found in 20 of 182 patients (11%) versus

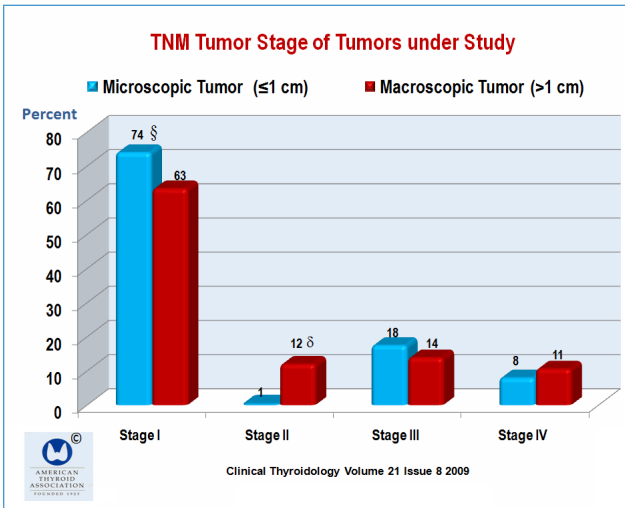

Figure 4. TNM tumor stages in this study. †P <0.001, comparing microscopic and macroscopic tumors. §P = 0.04 and δP<0.02, comparing microscopic and macroscopic tumors. Derived from data in Table 2 of Tzvetov et al. Stage III and IV were not significantly different in the microscopic and macroscopic tumor groups.

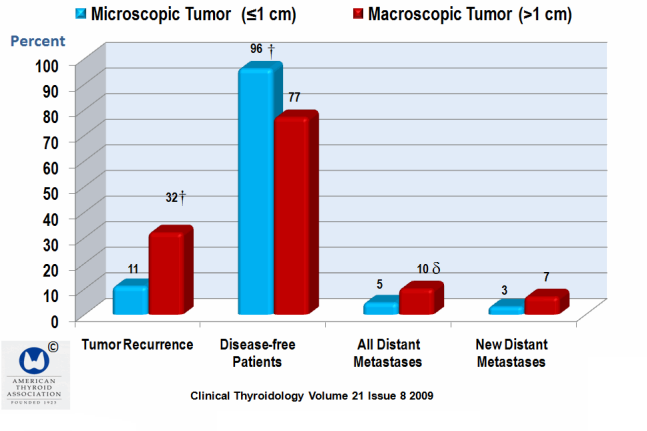

Figure 5. This figure shows overall rates of tumor recurrence, disease-free outcomes, all distant metastases, and new distant metastases. †P <0.001. δP < 0.02. Adapted from Figure 2 of Tzvetov et al. There were no significant differences in the rates of new distant metastases in the two groups.

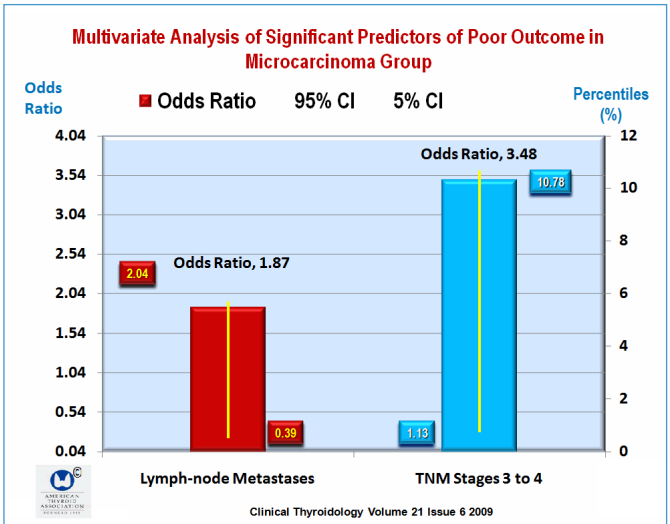

Figure 6. Multivariate analysis found only two parameters that were significant predictors of an adverse outcome in the microcarcinoma group: lymph-node metastases (OR, 1.87; 95% confidence interval [CI], 2.04 to 0.39) and TNM stages III to IV (OR, 3.48, 95% CI, 1.13 to 10.74). Also, lymph-node metastasis at initial diagnosis was correlated with young age (P = 0.001), male sex (P = 0.03), and tumor multifocality (P = 0.001).

151 of 474 (32%) patients with microscopic and macroscopic tumors, (P<0.001); overall, distant metastases were found in 10 of 225 patients with microscopic disease (5%) versus 54 of 543 patients (10%) with macroscopic disease (P = 0.02). New distant metastases were found in 5 patients with microcarcinomas; 5 were in the lung, 3 were in bone, and for 1 patient each tumor was in the liver and skin, as compared with 31 in the lung, 5 in the bone, 2 in the brain, and 1 in the adrenal gland in patients with macroscopic tumors. At the end of follow-up, 216 patients (96%) in the microscopic and 543 (77%) in the macroscopic tumor group were disease-free (P<0.001) (Figure 5). Of 10 patients with distant metastases who initially had microscopic tumors, 6 had classic papillary thyroid cancer or follicular variant papillary cancer. The site of distant metastases in this group was the lung with or without bone metastases; the other 4 had lung metastases from follicular thyroid cancer, which in some cases also involved bone, liver, or skin.

Univariate analysis found that lymph-node metastases and distant metastases were the only two variables associated with an unfavorable outcome in patients with microcarcinomas. On multivariate analysis using stepwise logistic regression, the only two tumor features found to be significant predictors of a poor outcome were lymph-node metastases (odds ratio [OR], 1.87; 95% confidence interval [CI]2.04 to 0.39,) (Figure 6), and TNM stages III to IV (OR, 3.48; 95% CI, 1.13 to 10.74) (Figure 6). Lymph-node metastases at the time of initial diagnosis were correlated with younger age (P = 0.001), male sex (P = 0.03), and tumor multifocality (P = 0.001). Distant metastases and ^{131}I therapy were excluded from the model because both were highly correlated with outcome.

CONCLUSION Lymph-node metastases and TNM stage independently portend an unfavorable prognosis in patients with well-differentiated thyroid microcarcinoma of various histologies.

COMMENTARY

Although the steady increase in thyroid cancers smaller than 2 cm is generally regarded to be a result of the widespread use of neck ultrasonography, there is reason to believe that this only partially accounts for this phenomenon, which has occurred around much of the world. The most widely quoted recent article on this subject is a study of the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database by Davies and Welch (1), who concluded that the increasing incidence of thyroid cancer in the United states is predominantly due to the increased detection of small papillary cancers by neck ultrasonography. They suggest that the growing incidence of thyroid cancer reflects an increased detection of subclinical disease, not an increase in the true occurrence of thyroid cancer. This article sparked several other similar studies.

An important study of the SEER database by Enewold et al. (2) concluded that medical surveillance and more sensitive diagnostic procedures cannot entirely account for the observed increases in papillary thyroid cancer rates, pointing out that among white women the rate of increase for papillary thyroid cancers >5 cm almost equaled that for the smallest cancers ≤1 cm. The authors suggested that other possible explanations for this phenomenon should be explored.

A more recent study of the SEER database by Chen et al. (3) found that the incidence rates of differentiated thyroid cancers of all sizes increased between 1988 and 2005 in both men and women. They found that the increased incidence rates across all tumor sizes suggests that increased diagnostic scrutiny is not the entire explanation for the increased rate of thyroid cancer in the past three decades. The authors concluded that other explanations, including environmental influences and molecular pathways, should be investigated.

A recent study from northwestern Spain (4) also found that the incidence of thyroid cancer has been increasing. The study found that this may reflect a contribution of other factors in addition to increased diagnostic activity, which may have contributed to the rising incidence of thyroid cancer in northwestern Spain. The authors suggested that additional studies are needed to explain this phenomenon, as there may be other unrecognized risk factors causing this problem.

Tzvetov et al. also suggest that ultrasound surveillance may account for the increased incidence of small thyroid cancers, although the study does not directly address this issue. The study compares the clinical course of well-differentiated microscopic thyroid cancers ≤1 cm with that of macroscopic tumors larger than 1 cm. Several aspects of this study bear close scrutiny. The patients with microscopic tumors were significantly older than those with macroscopic tumors, and the initial treatment was not uniform in the two groups. Total or subtotal thyroidectomy was performed in 98% of the patients with tumors larger than 1 cm, as compared with 77% of the patients with microcarcinomas. Also, ^{131}I was given to 16% of the patients with microcarcinomas and 23% of those with macrocarcinomas.

Tzvetov et al. conclude that the differences among patients with microscopic DTC and those with macroscopic tumors may not justify a different therapeutic approach. However, there are data suggesting otherwise. Six articles were cited by Tzvetov et al., that showed recurrence rates ranging from 11% to as low as 1.7% in studies by other authors, including Roti et al. (5), Chow et al. (6) , Ito et al. (7), Noguchi et al(8). and Hay et al. (9). Perhaps the most extensive study concerning this issue is that by Bilimoria et al. (10), in which a total of 52,173 patients with papillary thyroid cancer were studied, and for whom the 10-year tumor recurrence rate was approximately 5% for tumors smaller than 1 cm and 7% for tumors 1 to 1.9 cm. Moreover, the 10-year cancer-specific mortality rate was 2% for papillary microcarcinomas <1 cm and almost 3% for tumors 1 to 1.9 cm. Yet among a subset of 15,547 patients with papillary thyroid cancers ranging from 1 to 2 cm, those with lobectomy experienced a 24% higher risk for recurrence (P = 0.04) and a 49% higher 10-year thyroid cancer mortality rate as compared with patients who were treated with total thyroidectomy. The study also found that there was no significant difference in recurrence or survival rates between lobectomy and total thyroidectomy for patients with papillary thyroid cancers <1 cm in diameter. This conclusion parallels the recent recommendation made in the ATA guidelines for the management of papillary thyroid cancer.

— Ernest L. Mazzaferri, MD, MACP

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