Angiolymphatic tumor invasion is the main predictor of recurrence for papillary thyroid microcarcinoma

Arora N, Turbendian HK, Kato MA, Moo TA, Zarnegar R, Fahey TJ. Papillary thyroid carcinoma and microcarcinoma: is there a need to distinguish the two? Thyroid 2009;19:473-47.

SUMMARY

BACKGROUND Papillary thyroid microcarcinoma (PTMC) is defined as papillary cancer ≤1 cm, thus ranging in size from microscopic to as large as 1 cm in diameter. Some have suggested that tumors ranging in size from 1 to 5 mm have less aggressive clinical manifestations than tumors 6 to 10 mm in diameter. There is an even greater difference of opinion concerning the clinical behavior of classic papillary thyroid cancers (PTC) 1 to 2 cm or larger. The aim of this study was to compare classic PTC with PTMC.

METHODS The study subjects were patients with PTC referred to the New York Presbyterian Hospital–Cornell who had total or near-total thyroidectomy from January 1995 through January 2005 and had follow-up for at least 3 years after surgery. Patients with distant metastases unresponsive to ^{131}I therapy, or for whom clinical information was incomplete, were excluded from the study. PTMC was defined as a tumor ≤1 cm and PTC was defined as classic or follicular variant PTC. Incidental PTMC was defined as a tumor found during thyroid or neck surgery for conditions other than thyroid cancer, while nonincidental PTMC was defined as tumor that was resected in patients who had surgery for suspicious malignancy based on fine-needle aspiration biopsy (FNAB). Lymph-node metastases were identified either in the surgical histology specimens or on postoperative radioactive iodine imaging. Likewise, angiolymphatic invasion was defined by histologic evidence of tumor cell within a vessel, either attached to the vessel wall or associated with thrombosis. Extrathyroidal extension was defined as gross tumor extension found at surgery and confirmed on the surgical histology specimens.

RESULTS Of the 202 patients in the study, 66 (33%) had PTMC and 136 (67%) had PTC. There were 46 women (70%) with PTMC, the mean age of whom was 50 years (range, 24 to 78) as compared with a mean age of 46 years (range, 15 to 78) in the 136 patients with PTC. Complete tumor resection was accomplished in 59 patients (89%) with PTMC, and 115 patients (85%) with PTC. Approximately half of the patients in both the PTMC and the PTC group had central lymph-node dissections. Radioiodine therapy was given to 117 of the 136 patients (86%) with PTC and 44 of the 66 (67%) with PTMC (P<0.003).

Mean tumor size was 0.67 cm (range, 0.1 to 1) in the group with PTMC and 2.58 cm (range, 1.1 to 7) in the group with PTC. Multifocal tumor was found in 37 of 66 patients (56%) with PTMC and 71 (52%) with PTC. Extrathyroidal extension was found in 3 patients (4.5%) in the PTMC group and 19 (14%) in the PTC group. Angiolytic invasion was found in 4 (6%) of the PTMC group and in 18 (13%) of the PTC group. Except for average tumor size, all comparisons of PTMC and PTC were not statistically different.

Lymph-node metastases were found in 26 of 60 patients (43%) with PTMC and 63 of 124 patients (51%) with PTC (P = 0.35), and distant metastases were found in 3 of 47 patients (6%) with PTMC and 12 of 111 patients (11%) with PTC (P = 0.56). (Figure 1). Forty patients (19.8%) had tumor recurrence an average of 2.7 years after surgery (range, 6 months to 8.3 years). Tumor recurrence was found in 11 patients (17%) with PTMC and 29 patients (21.3%) with classic PTC (P = 0.57). The types of recurrence are shown in Figure 1. Approximately one third of recurrences in both groups were expressed only as a rise in

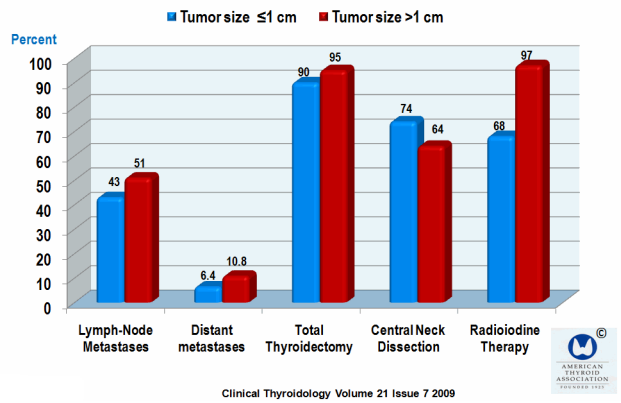

Figure 1. This figure shows the type of metastases, initial surgery, and ^{131}I therapy.

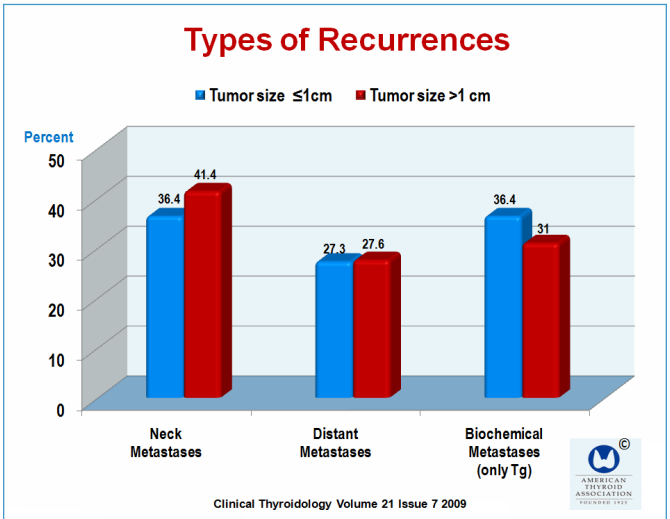

Figure 2. This figure summarizes the types of recurrences that occurred in patients with PTMC and PTC. None of the differences are statistically significant. Tg = Thyroglobulin.

serum thyroglobulin concentrations, with no identifiable source on imaging, while recurrence in the neck was the most common identifiable site in either group (Figure 2). There were several important differences in recurrence and disease-free outcomes among patients with PTMC and PTC. Tumors that recurred were significantly larger as compared with tumors that did not recur (0.81 cm vs. 0.64 cm, P<0.05); however, tumor size >8 mm was not found to be a significant marker for recurrence.

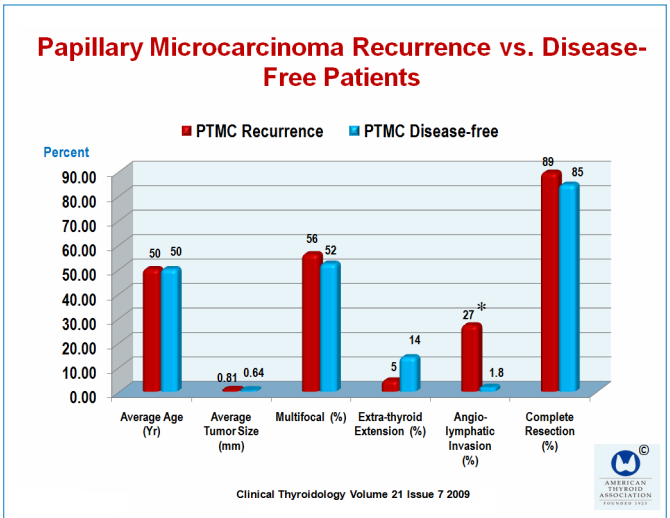

Figure 3. This figure shows that patients with PTMC had no significant difference in any of the parameters shown, except that 27% of patients with tumor recurrence had angiolymphatic invasion of tumor and only 2% who had angiolymphatic invasion remained free of disease (*P = 0.001)).

Among the patients with PTMC recurrence, tumors that recurred were significantly larger than those in patients who remained disease-free (8.1 mm vs. 6.4 mm, P<0.05), and patients with lymph-node metastases were significantly more likely to have angiolytic tumor invasion than those without lymph-node recurrence (3 of 11 [27%] vs. 1 of 55 [1.8]), respectively; P = 0.01).

None of the patients with incidental PTMC (n = 14) had tumor recurrence (P = 0.1), and tumors that recurred were more likely to be multifocal or to have lymph-node or distant metastases; however, this difference was not statistically significant (Figure 3). The types of recurrence in patients with PTMC and PTC were not significantly different. Multivariate logistic-regression analysis found that the presence of angiolymphatic invasion of PTMC was the only predictor of disease recurrence (P<0.02). However, the recurrence rates for PTMC and classic PTC were not significantly different (17% vs. 21%; P = 0.57)

CONCLUSION This study found that PTMC had a similar rate of poor prognostic features as compared with PTC, including lymph-node metastases and extrathyroidal extension, and recurrence rates in the two types of tumor were not significantly different. Angiolymphatic tumor invasion was the main predictor of recurrence.

COMMENTARY

This is an interesting study that compares the presentations and outcomes of patients with classic PTC and papillary microcarcinoma (PTMC). Before commenting on this paper, it is worthwhile to clarify the definition of papillary microcarcinoma, as it is not quite as clear as one might think. According to the World Health Organization (WHO) classification of tumors (1), the term microcarcinoma should be used for only papillary thyroid carcinoma that is found incidentally and that measures ≤1 cm in diameter. In some schemes, papillary carcinoma measuring <1 cm in diameter is considered a variant of papillary carcinoma (2-4). Also, the WHO definition concerning the caveat that this should be an incidentally discovered cancer, is more often than not considered in discussions of PTMC. The article by Arora uses the usual definition of PTMC without adding the term incidental. Of greater concern, the 6th edition of the TNM staging system endorsed by the American Joint Commission on Cancer (AJCC) (5, 6) and the International Union Against Cancer (UICC), which changed the definition of T1 from a tumor of ≤1 cm to a tumor of ≤2 cm, no longer is consistent with the WHO pathological definition of microcarcinoma. This only serves to add confusion concerning the management of papillary microcarcinoma.

Although there is debate concerning the management of PTMC, both the American and European Thyroid Associations (7, 8) suggest that lobectomy is sufficient therapy for patients with PTMC, providing the tumor is not multifocal, invasive or metastatic, or associated with familial papillary thyroid cancer in a patient who has not had head and neck irradiation. Still, there is a wide range of opinions concerning the management and general outcome of PTMC (9, 10). The tumor recurrence rates for PTMC are in the range of 5% (9, 11) 1 year after initial therapy (9), and the 10-year cancer-specific mortality rate in one of the largest studies published was 2% (11).

Yet over time, the recurrence rates of PTMC may be even higher than 5%. A study by Noguchi et al. (12) of 2070 patients with PTMC concluded that PTMC is essentially very similar to PTC that is ≥11 mm and has a very good prognosis. Smaller tumors and younger patients had a better prognosis. Among tumors ranging from 6 to 10 mm, the recurrence rates were 14% at 35 years, as compared with 3.3% in patients with smaller tumors. Patients older than 55 years had recurrence rates of 40% at 30 years, which is worse than those found in younger patients, who have a recurrence rates of less than 10%. Extracapsular invasion by the primary tumor also was found to have a higher recurrence rate. The authors of the study concluded that papillary microcarcinoma is similar to larger papillary carcinomas with tumor characteristics and age-based recurrence rates that extend for many years, justifying long surveillance after surgery.

The main findings of Arora et al. were an overall recurrence rate of approximately 20%; it was 17% in patients with PTMC. Tumors that recurred were significantly larger as compared with those that did not recur, fitting in with the notion that there is a range of outcomes in tumors ranging from 1 to 10 mm. None of the patients with incidental PTMCs had recurrence, suggesting that these tumors are less virulent than tumors that are apparent

at the time of diagnosis. The main finding of the multivariate analysis was that angiolymphatic tumor invasion portends a high rate of tumor recurrence, much like the findings reported by Noguchi et al.

Lastly, it should not go unnoticed that although all of the patients in this study had total thyroidectomy, approximately half had central compartment lymph-node dissection, and 68% with PTMC had postoperative ^{131}I therapy, yet about 20% of patients still had tumor recurrence.

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