

# Papillary microcarcinomas without unfavorable features may be candidates for observation alone

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## SUMMARY

### BACKGROUND

Neck ultrasonography and ultrasound-guided fine-needle aspiration biopsy has substantially altered the approach to the diagnosis of thyroid cancer, which has facilitated the identification of a large number of papillary microcarcinomas (PTMC) of uncertain long-term risk. This has prompted some to forgo surgery for PTMC unless there are unfavorable tumor features portending a poor prognosis. This is a prospective follow-up study of patients with PTMC who selected to forgo surgery. The authors started this observational trial in 1993, and in 2003 published their first report on 162 patients with PTMC who had observation alone, in whom 70% had no change in their tumors and 1.2% developed lymph-node metastases. The present study reports the most recent data on patients who participated in this trial.

### METHODS

Between 1993 through 2004, a diagnosis of PTMC was made after ultrasound screening and fine-needle aspiration biopsy in 1395 patients, 1055 of whom had immediate surgery, and 340 of whom were enrolled in the observation group after being given the option of not having surgery. Postoperative follow-up included ultrasonography and chest roentgenography or computed tomography scan more than once per year, and 52 patients had radioiodine a whole-body scan using 3 to 13 mCi, none of whom had abnormal <sup>131</sup>I uptake except in the thyroid bed. Tumor enlargement was defined as an increase in tumor size of 3 mm or more from the time of diagnosis.

However, when tumors developed unfavorable features such as tumor adjacent to the trachea or the dorsal surface of the thyroid, possible tumor invasion of the recurrent laryngeal nerve, clinically apparent lymph-node metastasis, high-grade malignancy on fine-needle aspiration biopsy or signs of tumor progression were recommended to have surgery.

### RESULTS

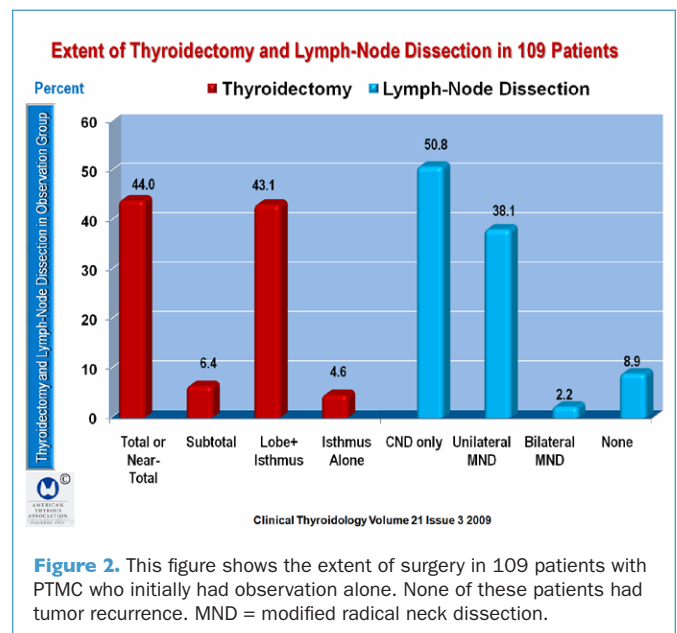
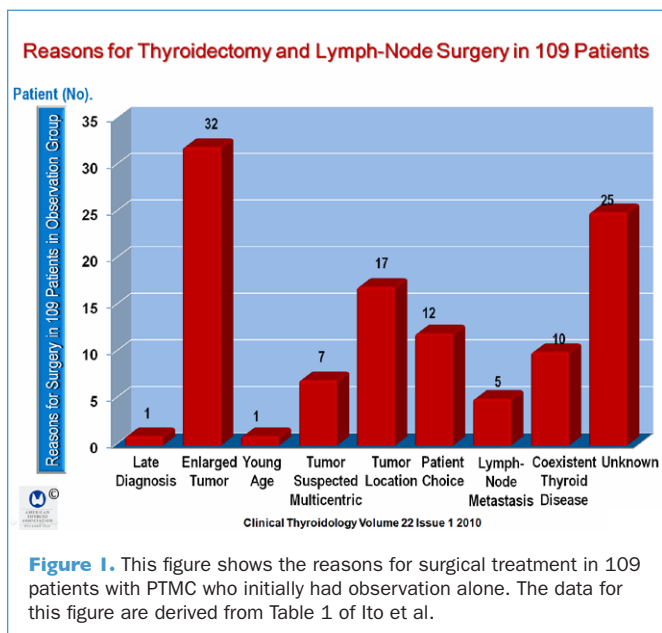
#### The immediate surgery and the long-term observation groups

In the immediate surgery group, 2 patients were found to have distant metastases at the time of initial diagnosis and were excluded from the study. The final immediate surgery group comprised 1059 patients, 964 women (91%) and 95 (9%) men whose mean age was 52 years (range 15 to 84).

In the observation group, 340 patients, 314 women (92%) and 26 men (8%) had follow-up for periods ranging from 18 through 187 months, during which they were enrolled in the observation group; however, after an average of 51 months of observation, (range 18 to 175), 109 (32%) of this group required surgery. Of the 109 patients, 102 were women (94%) and 7 were men (6%).

#### Surgery in 109 patients in the observation group (Figures 1 and 2)

109 patients in the observation group (32%) who required surgery had it for the following reasons: five had developed new lymph-node metastases (5%), 1 had surgery because of young age (1%), 7 for suspicion of tumor multicentricity (6%), 17 for tumor near the dorsal surface (11%), 10 for coexistent thyroid



disease (9%) and 25 for unknown reasons (23%) (Figure 1). The extent of thyroid and lymph-node surgery was considerably different among the 109 patients; all but 2 had thyroid surgery ranging from total thyroidectomy to isthmusectomy alone, and lymph node compartment dissection was performed in all but one patient, using complete radical neck dissection (CND) in 79 (72.5%) patients, unilateral modified radical neck dissection (MND) in 26 patients (3%) and bilateral MND in 2 patients (1.8%).(Figure 2) None of the 109 patients in the observation group who had surgery developed tumor recurrence.

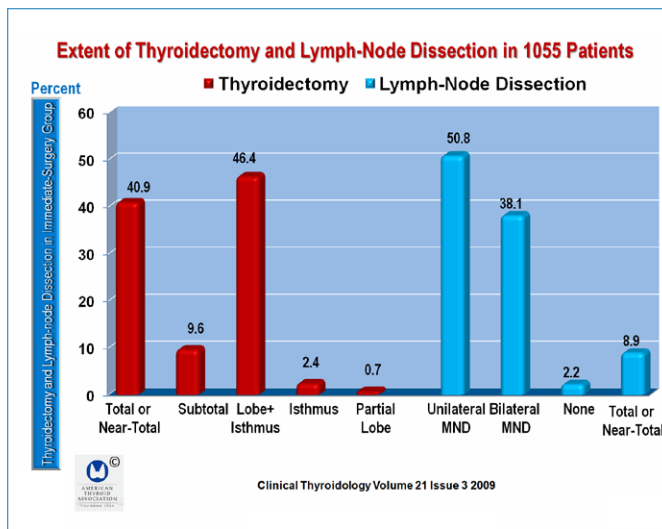
**Surgery in 1,055 patients in the immediate surgery group (Figure 3)**

In the immediate surgery group, thyroid surgery was total or near total thyroidectomy in 432 patients (40.9%), subtotal

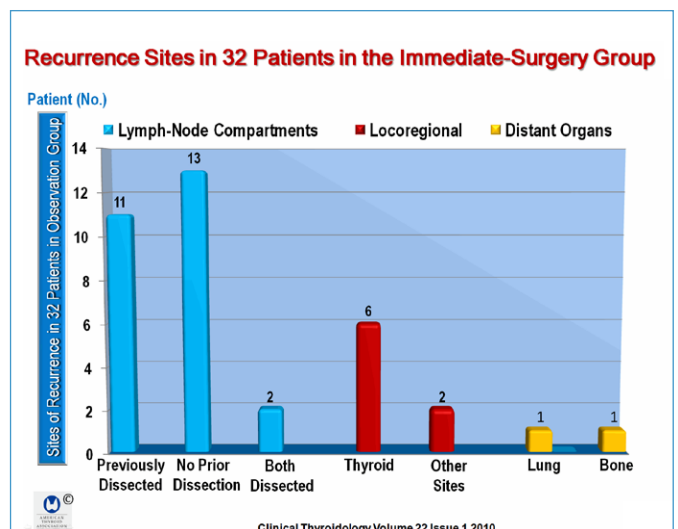
thyroidectomy in 101 (6%), lobectomy with isthmusectomy in 490 (46.4%), isthmusectomy in 25 (2.4%) and partial lobectomy in 7 (0.7%) (Figure 3) In this group, 32 patients had a recurrence. Clinically apparent lateral node metastasis (N1b) and male gender were recognized as independent prognostic factors of disease-free survival.

**Sites of tumor recurrence in 1,005 patients in the immediate surgery group (Figure 4)**

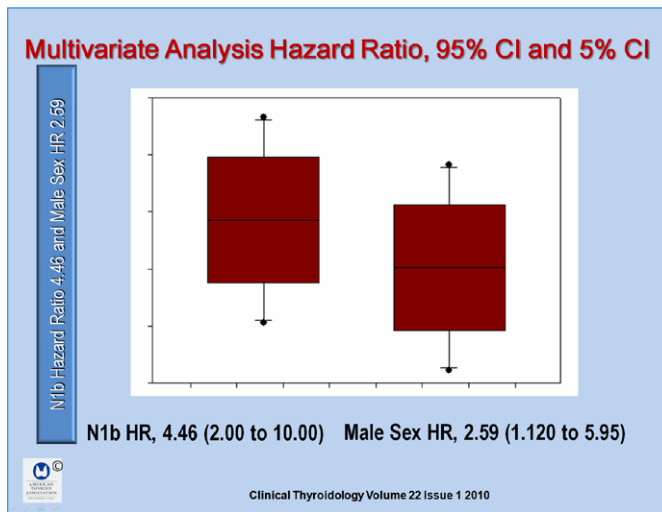
Tumor recurrence was found in 32 patients (3.0%). The organs involved with tumor recurrence were lymph nodes in 26 patients (2.5%). Among those who had lymph node tumor recurrences, 11 had previously dissected compartments, 13 had neck compartments that had not been dissected, and 2 had both lymph node compartments dissected. Locoregional



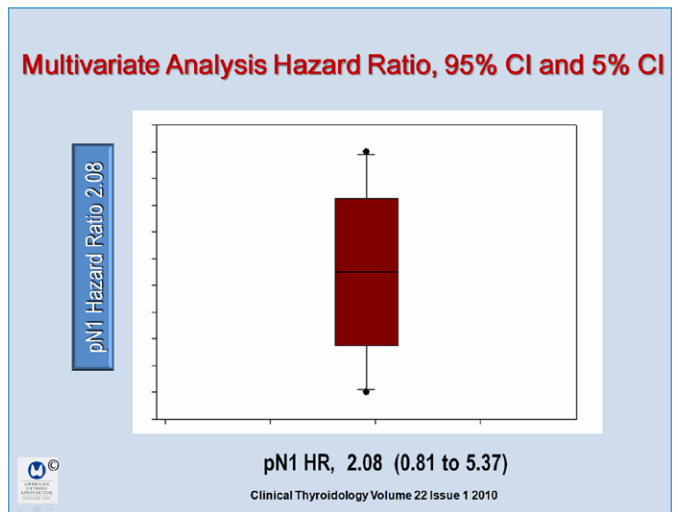
**Figure 3.** This figure shows the extent of thyroidectomy and lymph-node dissection in 1055 patients in the immediate surgical treatment group. The data for this figure are derived from Table 3 of Ito et al.



**Figure 4.** This figure shows the recurrence sites in 32 patients (0.3%). The data for this figure are derived from Table 4 of Ito et al.



**Figure 5 (A).** This figure shows the results of Cox multivariate analysis regarding disease-free survival. The data for this figure are derived from Table 5 of Ito et al. HR = hazard ratio, N1b = metastases in bilateral, midline or contralateral cervical or mediastinal lymph nodes.



**Figure 5 (B).** pN1 = metastases in ipsilateral cervical lymph nodes. The independent variables influencing disease-free survival were N1b tumors, male sex, and pN1, although patients with NO did not differ from that of patients with N1a. Male sex, P ≤0.0001.

organs involved the thyroid in 6 patients, (0.6%), and other sites in 2; distant metastases involved the lung in 1 patient and bone in another patient. (Figure 4) In patients who underwent immediate surgical treatment, clinically apparent lateral node metastasis (N1b) and male gender were recognized as independent prognostic factors of disease-free survival (Figure 5)

Analysis of this group found that sex, age, tumor size, multicentricity, TSH suppression, serum thyroglobulin levels or the presence of antithyroid antibodies had no significant bearing on tumor growth. Although patients aged  $\leq 45$  yr tended to have more tumor enlargement than those older than 45 yr, the difference was not statistically significant ( $P = 0.0624$ ).

#### Cox multivariate Analysis independent variables predicting disease-free survival (Figure 5)

Cox multivariate analysis found disease-free survival was worsened by N1b lymph-node metastases; Hazard Ratio (HR) with 95% confidence intervals (95% CI) were HR 4.46 95% CI 2.0 to 10.00,  $P = 0.0003$ ); male gender HR 2.59 95% CI 1.12 to 5.95;  $P = 0.255$ ) and clinically apparent pN1 metastases HR 2.08 95% CI 0.81 to 5.38. (Figure 5).

#### CONCLUSION

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#### COMMENTARY

In 1993, Ito et al. (1) began performing ultrasound screening with fine-needle aspiration biopsy, which by 2001 identified 732 patients with PTMC. As a consequence of the uncertainty surrounding the treatment of patients with such small tumors, the authors initiated a study in which patients were offered the option of observation alone without surgical therapy. In response, 162 of the 732 patients chose observation (22%) and 570 opted for immediate surgery (78%). During follow-up, more than 70% of tumors in the observation group either did not change or decreased in size as compared with tumor size at the time of diagnosis and, 10.2% of the other tumors enlarged by more than 10 mm. During this time, 56 patients in the observation group (35%) had surgery and were subsequently classified as the surgical treatment group. Of these 626 patients, lymph node dissection was performed in 594, and metastases were histologically confirmed in 50.5%. Also, multiple tumors were found in almost 43% of the patients. The tumor recurrence rate 2.7% at 5 years and 5.0% at 8 years after surgery, but none of the 109 patients in the observation group had recurrences after surgery. The authors opined that the preliminary data suggest that PTMC tumors do not frequently become clinically apparent, and that patients can choose observation while their tumors are not progressing, with the caveats that these tumors often are multifocal and further observation is necessary.

In 2007, Ito et al. published a review of this problem (2), noting that in their studies only 6.7% of PTMCs had enlarged by 3.0 mm or more in diameter during 5 years of follow-up, and that nodal metastases had become detectable in 1.7% of the patients in this study. They concluded that observation without surgery could be an attractive alternative for patients with low-risk PMCT, with the caveat that occult PMCT with lymph-node metastases may serve as the origin of distant metastasis, which has a more serious prognosis.

The main conclusion of the current study by Ito et al is that patients with PTMC can be candidates for observation, providing the tumor is not associated with unfavorable features, and regardless of patient demographic and clinical features, it would

not be too late for thyroid surgery, and should include modified neck dissection for N1b tumors.

There are several important features of the Ito study that warrant comment. First, none of the patient features were linked to tumor enlargement or lymph-node metastases, including male gender, tumor multicentricity, and advanced age and tumor size. Two patients in this study had distant metastases, 1 in lung and the other in bone.

A study by Noguchi et al (3) of 2070 patients with PTMC—which is the largest report of PTMC and the greatest long-term follow-up study of PTMC in the literature (median 15.1, mean 16.5 years)—found that that prognosis is better with smaller tumors (<6 mm) than larger tumors (6 to 10 mm). Recurrence rates after a 35 year follow-up were 14% in patients with larger tumors and 3% in those with smaller tumors. Moreover, 40% of patients older than 55 yr were found to have 30-year recurrence rates of 40%, which is worse than that in younger patients who had a tumor recurrence rate of less than 10%. Noguchi et al. found that extracapsular invasion of the primary PTMC has a high recurrence than that of tumors without this feature. Although the majority of recurrences in this study were in the neck, 73 patients had recurrences, 12 of which were distant metastases (1 lung, 4 bone 1 mediastinum and 1 multiple sites) after a median follow-up of 10.29 years. The authors concluded that PTMC is similar to larger papillary carcinomas with tumor characteristics and age-based recurrence rates that extend over many years. However, the independent risk factors on Cox proportional hazard model found the following were independent variables for outcome: autoimmunity  $p < 0.0001$ , gross nodal metastases  $p < 0.004$ , maximum primary tumor diameter  $P < 0.004$  and adhesion to the esophagus  $P < 0.03$ , and sex  $p < 0.14$ ; however, age at surgery was not an independent factor predicting outcome.

A study by Bilimoria et al (4) found the extent of surgery (total thyroidectomy) did not impact recurrence or survival for PTMC, whereas patients with tumor  $\geq 1$  cm treated with total thyroidectomy resulted in a significantly lower risk of recurrence ( $P = 0.04$ ) and death ( $P = 0.04$ ). This large study found the 10-year recurrence rate was 5% and the 10-year cancer-specific

mortality rate was 2% at 10 years. Both are somewhat higher than those reported by Ito and Noguchi.

The current study by Ito et al. has several features that warrant further comment. The observation cohort had patients with aggressive disease that required surgery, after which the patients were assigned to the surgical group. This likely alters the statistics concerning both the observation and surgery groups, and appears to change the conclusion of this study. The second is that most of the patients in these studies have had total thyroidectomy often with lymph-node compartment dissection, neither of which is recommended as primary therapy for PTMC by the ATA guidelines(5) and the European consensus for the management of differentiated thyroid cancer(6).

Although lobectomy is the optimal therapy for patients with PTMC, multiple lymph-node metastases are often found after total thyroidectomy and extensive lymph-node compartment dissection, which may require further therapy with radioiodine. (7;8) Still, it is not certain whether this impacts long-term outcome.

By all measures, the decision for treatment of small papillary thyroid cancers rests in the hands of the final arbitrator: The Patient.

— Ernest L. Mazzaferri, MD, MACP

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