

Patients with papillary microcarcinoma that extends into soft tissues or is metastatic to locoregional lymph nodes are at high risk for persistent or recurrent disease

Mercante G, Frasoldati A, Pedroni C, Formisano D, Renna L, Piana S, Gardini G, Valcavi R, Barbieri V. Prognostic factors affecting neck lymph node recurrence and distant metastasis in papillary microcarcinoma of the thyroid: results of a study in 445 patients. *Thyroid* 19:1-10.1089/thy.4-6-2009.0270 [doi]

SUMMARY

BACKGROUND The initial management of papillary thyroid microcarcinoma (PTMC) is controversial, mainly because the 10-year cancer-specific mortality rates with this tumor are vanishingly small, in the range of 1% to 2%. This study is aimed at defining the clinical course of this disease and the prognostic factors for tumor recurrence and distant metastases.

METHODS The study subjects were patients with PTMC selected from a group of 1030 patients surgically treated for papillary thyroid carcinoma in the Department of Otolaryngology in the Thyroid Disease Center in Reggio Emilia, Italy, from 1978 through 2003. PTMC was defined as a tumor ≤ 1 cm as described by the World Health Organization classification and documented in the final surgical histology. All patients were initially treated with total thyroidectomy or lobectomy plus isthmusectomy (partial thyroidectomy) and had completion thyroidectomy if at least one of the following was present: age ≥ 45 years, tumor multifocality, extrathyroidal extension, lymph-node metastases, or aggressive histologic variants of papillary thyroid cancer such as columnar cell, tall cell, or solid tumor. Partial thyroidectomy was performed only in patients younger than 45 years and without tumor multifocality, extrathyroidal extension, and lymph-node metastases or without aggressive histologic variants. Beginning in 1993, all patients had neck ultrasonography for presurgical assessment of cervical lymph-node metastases. Prior to 1996, level VI cervical lymph-node compartment dissections were performed only when lymph-node metastases were identified preoperatively or during surgery; however, after 1996 all patients with presurgical cytologic evidence of PTMC had total thyroidectomy with pretracheal and ipsilateral paratracheal lymph-node dissection if a frozen-section specimen revealed metastases in a dissected lymph node. Patients with lymph-node metastases in the lateral compartments underwent a modified neck dissection in cervical lymph-node-compartment levels II and IV. Thyroid capsular invasion was defined as tumor extension into the surrounding soft tissues or the sternothyroid muscle. Thyroid extracapsular invasion was defined as a tumor infiltrating the thyroid capsule with invasion of the perithyroidal soft tissues or muscle. All patients had radioactive iodine (^{131}I) remnant ablation with 30 to 50 mCi (1110 to 1850 MBq). Nine to 12 months later, serum thyroglobulin (Tg) levels were measured and a diagnostic whole-body ^{131}I scan was performed after thyrotropin (TSH) withdrawal or recombinant human TSH injection to confirm successful ablation of thyroid remnants. During the first 5 years after initial treatment, follow-up was performed every 6 to 2 months, and every 12 to 24 months thereafter. Beginning in 1994, cervical ultrasonography was performed during follow-up. Patients were classified as being free of tumor if they had undetectable TSH-stimulated serum Tg levels without evidence of lymph-node metastases by ultrasonography and whole-body ^{131}I scintigraphy.

RESULTS The study population comprised 445 patients; 347 women (78%) and 98 men (22%). In 222 (49.9%) of the patients PTMC was diagnosed preoperatively by fine-needle aspiration biopsy, and in the other 223 cases (50.1%) the tumor

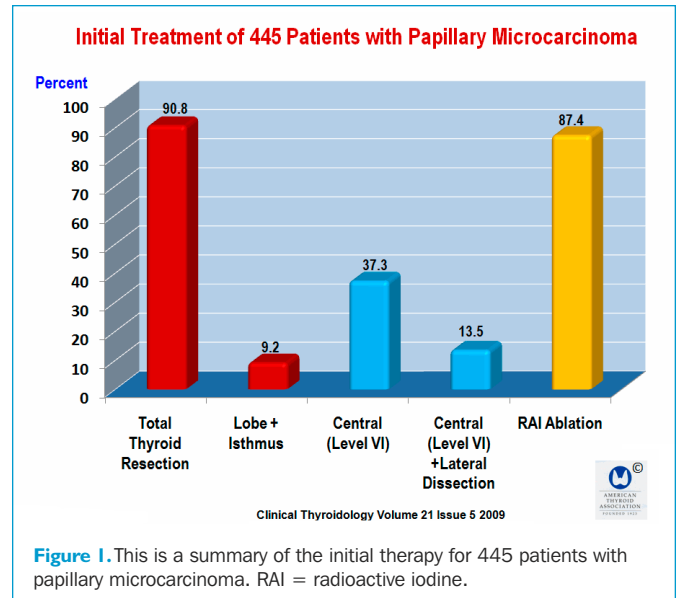


Figure 1. This is a summary of the initial therapy for 445 patients with papillary microcarcinoma. RAI = radioactive iodine.

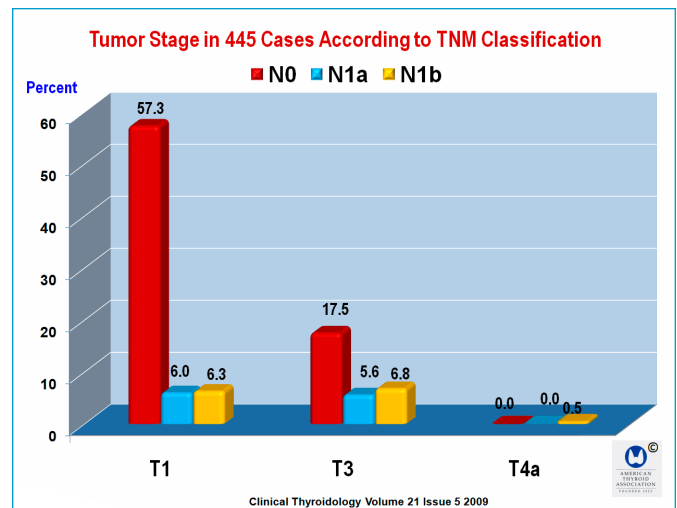


Figure 2. This is a summary of the tumor stage in 445 patients. pT1 = tumor 2 cm or less in greatest dimension limited to the thyroid gland; N0 = no lymph-node metastases; N1a = ipsilateral lymph-node metastases; N1b = metastases in bilateral, midline or contralateral or mediastinal lymph nodes; T₃ = tumor > 4 cm or any tumor with minimal extrathyroid extension; T_{4a} = tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve.

Figures 3 and 4. These figures show the characteristics of the study patients and tumor characteristics of the papillary microcarcinomas in this study.

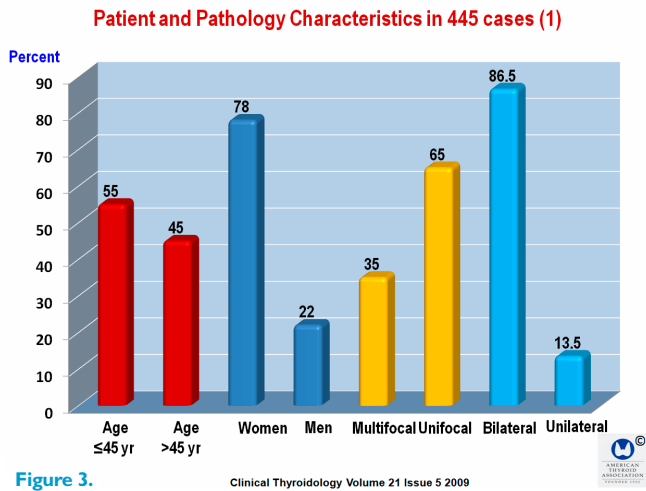


Figure 3.

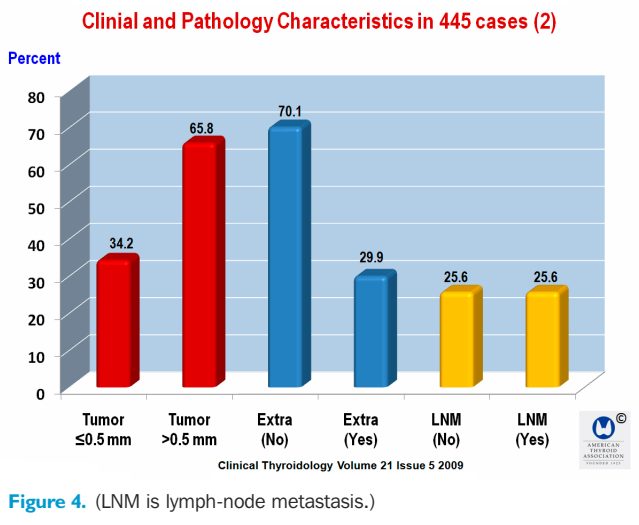


Figure 4. (LNM is lymph-node metastasis.)

was discovered in patients undergoing surgery for multinodular goiter (n = 103), follicular neoplasm (n = 99) or Graves' disease (n = 14). A total of 41 patients had partial thyroidectomy alone; total thyroidectomy was thus performed in 404 patients (90.8%) (Figure 1). Neck lymph-node compartment dissection was performed in 226 patients (49.7%), of whom 166 (73%) did not have presurgical evidence of lymph-node metastases but underwent a level VI (central) compartment dissection with total thyroidectomy, while 60 patients (27%) with presurgical evidence of cervical lymph-node metastases had central compartment and lateral neck dissection with total thyroidectomy (Figure 1). The tumor node, metastasis (TNM) stage distribution is shown in Figure 2. The patient characteristics and the clinical and pathologic characteristics of tumor are shown in Figures 3 and 4. The surgical histology showed that 312 patients (70.1%) had classic papillary thyroid cancer, 117 (26.3%) had follicular variant papillary thyroid cancer, 4 (0.9%) had follicular cancer, and 1 (0.9%) had papillary cancer with medullary thyroid cancer. After a mean follow-up of 5.3 years (range, 1 to 26), 17 patients (3.8%) had recurrence or persistent disease: neck recurrence was

Independent Risk Factors for Locoregional or Distant Tumor Recurrence as Determined by Multivariate Analysis

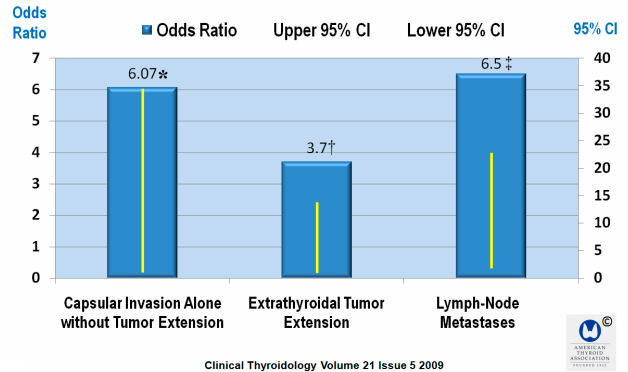


Figure 5. This figure shows a summary of the independent risk factors for locoregional recurrence or persistent tumor, with or without distant metastases. *P = 0.04, †P = 0.049, and ‡P = 0.003 for odds ratios. CI = confidence interval.

found in 12 patients (2.7%), distant metastases occurred in 4 patients (0.9%), and 1 patient had neck recurrence and distant metastases. Only 6 (46%) of the neck recurrences were identified by neck ultrasonography. One patient (0.2%) died of the disease.

Univariate analysis in the 389 patients eligible for statistical analysis found that the presence of extrathyroidal tumor extension (pT₃) with or without lymph-node metastases (NO or N1) at the time of diagnosis was related to locoregional cervical and distant tumor recurrences (P<0.05). The rate of tumor recurrence or persistent disease was observed more often in pT₃ as compared with pT₁ tumor stage (P = 0.02). The rate of tumor recurrence (11.6%) in patients with lymph-node metastases (N1) was significantly higher than the rate in patients without lymph-node metastases (pNO; P = 0.02). The rates of cervical and distant recurrences were more frequent in patients with thyroid tumor capsular invasion without extrathyroidal extension (8.1% vs. 3.6%), which was not statistically significant (P = 0.06). The rate of neck recurrence (0.9%) was the same in patients who underwent elective level VI dissection as compared with patients who did not undergo this procedure.

Multivariate analysis identified three independent prognostic risk factors related to the persistence or recurrence of locoregional PTMC tumor with or without distant metastasis, which were as follows: (a) a sixfold risk for recurrence with capsular invasion without extrathyroidal tumor extension (odds ratio [OR], 6.07; 95% confidence interval [CI], 1.06 to 34.5; P = 0.04); (b) a 3.7-fold risk for recurrence with extrathyroidal tumor extension at the time of diagnosis (OR, 3.7; 95% CI, 1 to 13.9; P = 0.049); and (c) a 6.5-fold risk for recurrence in patients with lymph-node metastases at the time of diagnosis (OR, 6.5; 95% CI, 1.8 to 22.9; P = 0.003) (Figure 5). Age, sex, tumor bilaterality, and tumor diameter >5 mm or ≤5 mm were not significant factors for recurrence.

CONCLUSION Patients with papillary microcarcinoma that extends into the thyroid capsule, with or without extrathyroidal tumor extension or with lymph-node metastases, are at higher than usual risk for tumor recurrence or persistence of disease that should be treated with total thyroidectomy and radioiodine therapy.

COMMENTARY

Papillary microcarcinomas comprise almost half of the thyroid cancers that have been diagnosed in the United States during the past three decades (1). The sheer numbers of these small tumors has sparked substantial debate, concerning initial management of papillary microcarcinoma, with opinions ranging from no therapy (watchful waiting) (2) or lobectomy alone for incidentally discovered papillary microcarcinomas, unless the tumor is multifocal, has aggressive histology (e.g., tall-cell carcinoma), is metastatic, or is found in patients with a history of head and neck irradiation or familial tumor (3), in which case total thyroidectomy is advised. Patients with papillary microcarcinoma are rarely treated with radioiodine (¹³¹I), although tumor that is aggressive, invasive, and metastatic would prompt some to suggest ¹³¹I therapy (4,5). The nuances concerning the features and management of these small tumors have sparked much of the debate.

One of the issues that seems to be disregarded regularly is the nuances concerning the definition of papillary microcarcinoma and the risk for poor outcome. The World Health Organization's definition of papillary microcarcinoma is a papillary tumor, which is found incidentally, that measures 1 cm or less in diameter. Many authors ignore the fact that papillary microcarcinoma, by definition, is a tumor that is found incidentally (6). The second problem relates to staging risk for papillary microcarcinomas. The sixth edition of TNM staging system, which is endorsed by the American Joint Commission on Cancer and the International Union Against Cancer have changed the definition of T1 from a tumor of 1 cm or less in diameter to a tumor of 2 cm or less, which renders the pathological definition of papillary microcarcinoma no longer consistent with the WHO pathological definition, according to the WHO classification of tumors (6). Moreover, the TNM definition of stage I papillary thyroid cancer in a patient younger than 45 years is a tumor of any size, with or without lymph-node metastases, in effect rendering locoregional lymph-node metastases of no prognostic importance. Most patients would not agree with this definition.

Why are these issues important? A seminal study by Bilimoria et al (7) of slightly over 52,000 patients with papillary cancer, among whom 12,469 had tumors <1 cm, found that 10-year recurrence rates for these subcentimeter tumors were 4.6% and the 10-year cancer-specific mortality rate was 2%. However, there was little information about tumor invasion or lymph-node metastases in the group with subcentimeter tumors. The main outcome concerning this group of tumors was that total thyroidectomy did not confer an advantage measured in terms of recurrence and cancer-specific mortality.

A study by Noguchi et al. (8) of 2070 patients with papillary microcarcinoma in which the median follow-up was 15.1 years and was as long as 35 years in some patients provides important information on tumor recurrence. The main findings were that the 30-year recurrence rates were 40% in patients older than 55 years. Multivariate analysis found that four variables independently predicted recurrence: (a) absence of autoimmune thyroid disease, (b) gross lymph-node metastases, (c) tumor size >5 to 10 mm, and (d) esophageal tumor invasion. The 35-year recurrence rates were 3% for tumors 1 to 5 mm, and 14% for tumors 6 to 10 mm

($P < 0.001$). The recurrence rates were 20% and 5%, for patients with and without gross lymph-node metastases ($P < 0.001$); and the recurrence rates were 40% and 6%, for patients with and without esophageal tumor invasion ($P < 0.001$). The number of grossly enlarged lymph nodes was inversely related to recurrence-free survival. The 30-year recurrence rates were less than 10% in patients younger than 55 years and 40% for patients 55 years or older. The main conclusion of this study was that papillary microcarcinomas larger than 5 mm that are invasive and metastatic have a high recurrence rate, especially among older patients without thyroid autoimmune disease.

A recent meta-analysis of papillary microcarcinoma by Roti et al. (9) found that tumor recurrence was significantly associated with age <45 years ($P < 0.04$) and with clinically overt papillary microcarcinomas ($P < 0.001$, but was not related to tumor size) but tumor multifocality and lymph-node metastases at the time of diagnosis were highly significant factors related to recurrence ($P < 0.001$).

There is relatively little information about the efficacy of lymph-node dissection in patients with papillary microcarcinoma. Mercante et al. performed neck lymph-node compartment dissection in 226 patients (50%), of whom 166 (73%) did not have presurgical evidence of lymph-node metastases but had a total thyroidectomy with prophylactic level VI (central) cervical compartment dissection, while 60 (27%) others with presurgical evidence of cervical lymph-node metastases had total thyroidectomy with therapeutic central compartment and lateral neck dissections. It is difficult to identify the effect of initial therapy—thyroid surgery, lymph-node compartment dissections, and radioiodine therapy—in a group of patients with papillary microcarcinoma, half of whom had their tumor discovered during surgery for multinodular goiter ($n = 103$).

The American Thyroid Association guideline recommendations for initial therapy for patients with papillary microcarcinoma are as follows:

- R26: For patients with thyroid cancer larger than 1 cm, the initial surgical procedure should be a near-total or total thyroidectomy unless there are contraindications to this surgery. 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 nodal metastases. Recommendation A
- R27a1 Therapeutic central-compartment (level VI) neck dissection for patients with clinically involved central or lateral neck lymph nodes should accompany total thyroidectomy to provide clearance of disease from the central neck. Recommendation B
- R27b1 Prophylactic central-compartment neck dissection (ipsilateral or bilateral) may be performed in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes, especially for advanced primary tumors (T₃ or T₄). Recommendation C

- R27c1 Near-total or total thyroidectomy without prophylactic central neck dissection may be appropriate for small (T1 or T₂), noninvasive clinically node-negative papillary thyroid cancers, and most follicular cancer. Recommendation C

These recommendations provide guidance for the spectrum of initial findings in patients with papillary microcarcinoma.

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