Approach to the Patient with Incidental Papillary Microcarcinoma

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Analysis of the Surveillance Epidemiology and End Results database reveals that since 1995 a 2.4-fold increase in thyroid cancer has occurred. A concomitant rise in cases of thyroid microcarcinoma has also been noted, with the frequency rising by approximately 50% as well. Increased detection of thyroid nodules, many of them below 1 cm in size, is at least partly responsible for this trend. The wide use of sensitive imaging modalities for various indications leads to the incidental discovery of thyroid nodules, some of which contain thyroid cancer, including cases of microcarcinoma. Although the vast majority of patients with thyroid cancer foci smaller than 1 cm will do exceedingly well long term, exceptions do occur, with some patients experiencing recurrence either locally or less frequently with distant metastasis. There has been some debate on the optimal management for these patients to include: extent of surgery required, the usefulness of ablation with radioactive iodine, as well as the optimal level for TSH suppression. In this article, we will review the available data and recommendations surrounding the management of patients with incidental thyroid microcarcinoma **(*J Clin Endocrinol Metab* 95: 3586–3592, 2010)**

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Learning Objectives
Upon completion of this educational activity, participants should be able to
- Determine the appropriate extent of surgery based on various clinical parameters found in cases of thyroid microcarcinoma.
- Decide when radioactive iodine ablation is appropriate for patients with incidental microcarcinoma.
- Review risk-adjusted TSH suppression goals for thyroid microcarcinoma patients.
- Provide recommended follow-up management of patients with incidental microcarcinoma.

Target Audience
This continuing medical education activity should be of substantial interest to endocrinologists.
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A 40-yr-old female presents with a large multinodular goiter and complaints of some dyspnea and shortness of breath, especially in the supine position. The patient also reports a pressure sensation in her neck at times. Family history is notable for both mother and maternal grandmother having large benign goiters that required surgical removal. Physical examination reveals a coarse, enlarged thyroid gland. No cervical lymphadenopathy is present, but slight rightward tracheal deviation was noted. The physical examination was otherwise unremarkable. Thyroid function tests revealed a mildly suppressed TSH level of 0.13 μIU/ml (normal range, 0.27–4.20) with free T_4 of 1.10 ng/dl (0.89–1.76) and slightly elevated total T_3 of 183 ng/dl (60–181). Results from other labs include: antithyroglobulin antibody, 81 IU/ml (0–80); antithyroid peroxidase antibody, 1 IU/ml (0–20); thyroid-stimulating Ig, 90% (0–125%); and thyroid binding inhibitory Ig, 33% (0–16%). Technetium-99m thyroid scan revealed

Abbreviations: LT4, Levothyroxine; PTC, papillary thyroid carcinoma; RAI, radioactive iodine; TG, thyroglobulin; TMC, thyroid microcarcinoma; WBS, whole body scan.

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heterogeneous uptake with photopenic areas in the left and right midpoles as well as substernal extension with a 24-h radioactive iodine (RAI) uptake of 23% (8–30%). Thyroid ultrasound revealed a multinodular goiter with nodules (maximal diameter) as follows: right upper pole, 2.4 cm; right middle pole, 1.8 cm; right lower pole, 1.4 cm; left middle pole, 1.7 cm; and isthmus, 1.4 cm. The right lobe of the thyroid was measured at $5.3 \times 2.4 \times 3.4$ cm, whereas the left lobe was $9.4 \times 4.5 \times 4.4$ cm. Based on the size and ultrasound and scan characteristics of the nodules, fine-needle aspiration was performed on the right upper, right lower, and left middle pole nodules. Cytology revealed predominantly colloid with some benign-appearing follicular cells. A noncontrast neck computed tomography revealed heterogenous goiter with multiple nodules with mild tracheal deviation to the right. The patient was diagnosed with a toxic substernal nodular goiter complicated by Graves' disease. After a discussion of management options, the patient elected to proceed with a total thyroidectomy. The patient was started on methimazole 10 mg and, once euthyroid, underwent total thyroidectomy. Histology was consistent with a nodular goiter, but two foci of papillary thyroid cancer (PTC) of 1.5 and 0.5 mm were noted in the right lobe independent of the thyroid nodules detected on the preoperative ultrasound. No vascular or capsular invasion was noted, nor was there any cervical adenopathy evident by imaging or surgical inspection. After prolonged discussion of management options with the patient, it was decided to forgo RAI ablation and to start levothyroxine (LT4) therapy with a TSH goal of 0.5 to 1.0 μIU/ml. The patient is well and without evidence of disease 3 yr later.

In summary, this patient was found to have incidental, multifocal PTC with two foci confined to the right lobe within a toxic nodular goiter, with a positive thyroid binding inhibitory Ig titer consistent with underlying Graves' disease.

Epidemiology of Incidental Thyroid Microcarcinoma

Incidental thyroid microcarcinoma has also been referred to as occult carcinoma or incidental microcarcinoma. World Health Organization guidelines describe thyroid microcarcinoma (TMC) as tumors of less than 1 cm in size (1). They may be solitary, or multiple microfoci may be present. The medical meaning of the term "incidental" is actually not well standardized. It may imply that a microcarcinoma was uncovered in a thyroid nodule found incidentally during testing for another matter or that the tumor was found in thyroid tissue outside of the nodule(s) being evaluated. Typically, the latter occurs with a thorough histological examination of the thyroid gland after surgical removal. In clinical practice, it is not uncommon to encounter cases where small, incidental foci of PTC are discovered during histological review of an otherwise benign multinodular goiter.

Autopsy studies have revealed that the occurrence of microcarcinoma (<10 mm), primarily foci of PTC, ranges between 6 and 36% (2–4). It has also been reported that the frequency of TMC has climbed from 19% between 1945 and 1955 to 35% between 1995 and 2004 (5). This trend corresponds with data from the Surveillance Epidemiology and End Results database that reveal a 2.4-fold rise in thyroid cancer incidence from 3.6 per 100,000 in 1973 to 8.7 per 100,000 in 2002, consisting primarily of PTC cases (6). Furthermore, between 1988 and 2002, a 49% (95% confidence interval, 47–51%) increase in tumors equal to or less than 1 cm was noted (6). It has been postulated that at least part of this rise of TMC is related to increased detection primarily due to the wide use of thyroid ultrasound, which allows for detection of small nonpalpable nodules. Additionally, other sensitive anatomic and scintigraphic imaging modalities, such as computed tomography, magnetic resonance imaging, and ^{18}F-fluorodeoxyglucose positron emission tomography scanning, can incidentally uncover thyroid nodules leading to further evaluation and detection of microcarcinoma in some instances.

Presentation of Thyroid Microcarcinoma

As the term incidental implies, these TMCs are discovered by happenstance and so typically are without any corresponding symptoms. The majority of TMCs are foci of PTC (Table 1), although follicular TMCs occur as well. The average size of a TMC is about 6 mm, and by definition the size does not exceed 1 cm (5). Multiple foci can be found limited to one lobe or may be present bilaterally. Available data have shown that these lesions may repre-

TABLE 1. Presenting characteristics of thyroid microcarcinomas

Characteristic	Expected range of occurrence
Mean primary tumor size (mm)	5–6
Multifocality	30–40
Bilaterality	20
Cervical lymph node	25–43
Extrathyroidal extension	15–21
Vascular invasion	~4
Distant metastasis	1.0–2.8

Data are expressed as percentage unless otherwise indicated. Expected size or rate of occurrence is based on available literature relating to thyroid microcarcinomas.

sent intraglandular metastasis or be independent foci of a separate clonal origin (7). The reported prevalence of multifocality varies but appears to be present in 30–40% of cases, whereas bilateral disease (*i.e.* disease in both lobes) is found in approximately 20% of involved glands (8, 9). Furthermore, additional concerning features can be seen in TMC cases. Cervical lymph adenopathy is discovered in 25 to 43% of patients with TMC. Extrathyroidal extension, primarily microscopic in nature, is noted in about 15–21%, whereas vascular invasion may be present in approximately 3.5%. Distant metastases occur infrequently at a rate of 1.0–2.8% (5, 8, 9).

Surgical Management

The example patient underwent a total thyroidectomy addressing both her underlying Graves' disease and bilateral nodularity. However, TMC is frequently uncovered on final histology in patients having undergone less than a total thyroidectomy. In cases where TMC is found after a hemilobectomy has been performed with or without isthmusectomy, one is obliged to consider the need for completion thyroidectomy (Table 2). When contemplating possible completion thyroidectomy in patients with TMC, it is important to consider any complicating factors in the decision-making process. Factors affecting the management of thyroid cancer patients include: the presence of bilateral nodularity, cervical lymph adenopathy, metastasis either local or distant, tumor multifocality, local invasion, having an aggressive subtype of PTC (tall cell, columnar, insular, poorly differentiated, diffuse sclerosing, *etc.*), older age, gender, family history of PTC, and the existence of underlying Graves' disease (10–14). The presence of any of these aforementioned factors provides varying levels of justification for proceeding with a more complete extent of thyroid removal.

TABLE 2. Recommendations for management of TMC

Isolated unifocal disease
Lobectomy ± isthmusectomy
RAI ablation, not recommended
TSH suppression goal[a]
Initial, 0.1–0.5 mU/liter
Long-term, 0.3–2.0 mU/liter
Multifocal disease
Near-total/total thyroidectomy
RAI ablation, individualize use (consider if complicating factors are present)
TSH suppression goal[a]
Initial, 0.1–0.5 mU/liter
Long-term, 0.3–2.0 mU/liter
Unifocal/multifocal disease with complicating factors[a]
Near-total/total thyroidectomy
RAI ablation, strongly consider
TSH suppression goal[a]
Initial, <0.1 mU/liter
Long-term, 0.1–0.5 mU/liter

Complicating factors consist of cervical lymphadenopathy, extrathyroidal invasion (especially gross invasion more so than microscopic), age greater than 45 yr, aggressive histological subtype, positive thyroid cancer family history, and/or distant metastasis.

[a] Adjust TSH suppression goal based on duration of disease-free state, assessed likelihood of recurrence, and individual risks assessment for tolerance of TSH suppression therapy.

Before pursuing completion surgery, one must assess the potential risks or benefits for such a course. It must be determined whether completion thyroidectomy will improve the patient's outcome. As far as mortality is concerned, the preponderance of data indicates that death related to TMC is exceedingly low, at less than 1%. Because survival with TMC does not appear significantly reduced, the focus on patient benefit shifts to any potential reduction in morbidity. Data from one large cohort of patients with TMC initially indicated a reduction in recurrence rates with "bilobar resections" in comparison to unilateral procedures (15). However, later reanalysis of this cohort, once it reached 900 patients observed over a 60-yr period, did not reveal any difference in recurrence rates related to extent of surgery (5). A second smaller study concurred with these findings (9). However, another study with 281 TMC patients followed for 7.3 yr revealed a significant reduction in recurrence rates with total thyroidectomy (36 *vs.* 70%) in comparison with lesser extent of resection (8). Data from the National Thyroid Cancer Treatment Cooperative Study Group Registry (NTCTCSR) found that with lobectomy, recurrences were more common with multifocal disease than unifocal lesions (18 *vs.* 4%) (16). Also, patients with multifocality undergoing resection of at least a near-total thyroidectomy had less recurrence than those with a less aggressive surgical approach.

The 2009 American Thyroid Association (ATA) guidelines addressing management of differentiated thyroid cancer indicate that patients with small (<1 cm) tumors that are unifocal and intrathyroidal without any lymph nodes or metastasis need not undergo completion thyroidectomy (16). However, the question is then, how should management differ when one of these aforementioned complicating factors is present?

Complicating Factors

Multifocality

Multiple foci are commonly found with PTC in general, and this stands true for cases of TMC as well. Patients with two or more foci in the resected lobe have an increased risk of additional foci in the contralateral lobe. Genetic analysis of multiple PTC foci in the same thyroid gland has revealed that whereas some of the foci have a shared der-

ivation, others are distinctly of an independent clonal origin (7). Therefore, some tumor foci may represent intraglandular spread, whereas others are independently developing foci. Multifocality has traditionally been considered an important predictor for recurrent disease. Indeed, the literature to date indicates that multifocality is associated with a higher rate of PTC recurrence. In one study, only 1.2% of patients with unifocal disease had recurrent cancer, whereas 8.6% with multifocal disease did (8). The extent of surgical resection appears relevant to the risk as well. In two studies, the recurrence rates for patients with multifocality undergoing total thyroidectomy were found to be 2.3–5%, whereas lobectomy and/or isthmusectomy yielded a higher rate of recurrence at 8.2–25% (8, 9). Of note, unifocal tumors managed with lobectomy and isthmusectomy had only a 3–4% recurrence (8, 16). Most recently, data from 611 patients with TMC included in the NTCTCSR revealed that 6.2% of patients had recurrent disease (17). Of patients that underwent less than a near-total thyroidectomy, there were more recurrences noted in cases with multifocal than unifocal disease. Also, a nonsignificant trend was reported toward fewer recurrences with multifocal cases that underwent total or near-total thyroidectomy than those with less complete surgery (6 *vs.* 18%; $P = 0.058$).

In addition, studies have revealed an almost 20% rate of contralateral lobe involvement with at least one other focus in patients initially thought to have a single focus of PTC before completion thyroidectomy (8). Multifocality also appears to be associated with an increased risk for locoregional lymph node involvement, with up to a 5.6-fold increase per one report (9). In a group of 281 TMC patients, seven of eight TMC patients presenting with distant metastasis were noted to also have multifocal disease (8).

In summary, multifocality is associated with a higher rate of recurrence. Available evidence is somewhat divided if total or near-total thyroidectomy reduces this risk of recurrence in comparison to patients receiving less aggressive resection.

Cervical lymph node involvement

As previously mentioned, cervical lymph node involvement is encountered in patients with TMC. When cervical lymphadenopathy is found at presentation, future lymph node recurrence is increased significantly, with a rate of about 11–22% in comparison to 0.8–6% in node-negative patients (5, 17). Additionally, data indicate a significant (11-fold) increase in risk for distant metastasis with the presence of cervical lymphadenopathy (9). The scope of lymph node involvement may modulate the risk for recurrence. Data from at least one study suggest that macroscopic lymph node involvement and/or the presence of extracapsular tumor invasion penetrating the lymph node capsule hold a higher risk for recurrence than subclinical lymphadenopathy discovered just on microscopic inspection (18). Another study found that patients presenting with palpable cervical lymphadenopathy had a recurrence rate of 16% after therapeutic node dissection in comparison to only 0.43% in a group of patients undergoing prophylactic lymph node dissection, of which 66% had evidence of lymph node involvement histologically (17). In at least one study, the use of modified radical neck dissection in TMC patients with ultrasonographically documented abnormal lymph nodes has been shown to potentially improve recurrence-free survival (19). Patients found to have abnormal cervical lymph nodes preoperatively, especially palpable nodes, should undergo therapeutic lymph node dissection.

Distant metastasis

The distant metastasis rate appears to be very low in TMC patients. The rate has been reported to be between 0.2 and 2.85%, based on three studies in patients with TMC (8, 9, 16). In general, patients with PTC and distant metastasis have a significantly worse prognosis than patients who do not; the same holds for those associated with TMC. These patients should be treated more aggressively to include the use of surgery, RAI ablation/treatment, and other available treatment modalities as indicated.

Graves' disease

Thyroid cancer, particularly PTC, has been reported to complicate Graves' disease in the range of 1 to 9% of cases (12). There has been concern that thyroid cancer may behave more aggressively in Graves' disease patients. The answer to this concern is clouded by the fact that many studies combined "occult" microcarcinomas with larger lesions in their analyses. Although Graves' disease may be associated with increased aggressiveness with tumors larger than 1 cm, this does not appear to be the case with microcarcinomas (20). In one report, patients with incidental TMC associated with Graves' disease actually did better than controls with a 99 *vs.* 93% 20-yr disease-free follow-up. However, the results are complicated by the fact that Graves' patients underwent near-total thyroidectomy, whereas lobectomy predominated in the controls. As far as cases of TMC, Graves' disease does not appear to be associated with any negative impact on prognosis.

Treatment

RAI

Postsurgical ablation with RAI is used to destroy any remaining thyroid remnant after total/near-total thyroid-

ectomy. An adjuvant tumoricidal effect on persistent thyroid cancer cells can occur as well. Radioactive ablation simplifies the follow-up of thyroid cancer patients by facilitating monitoring by whole body scan (WBS) and thyroglobulin (TG) levels. Also, WBS in conjunction with RAI ablation can be used to detect iodine-avid lesions such as cervical adenopathy or distant metastasis. However, recent data have brought into doubt the efficacy of RAI in patients with low-risk disease. Present treatment guidelines by the National Comprehensive Cancer Network (NCCN) and ATA indicate that uncomplicated American Joint Committee on Cancer stage I patients with a nonaggressive form of PTC (unifocal and without locoregional extension or invasion) need not receive RAI ablation (21). Many TMC cases would fall under this category. The recommendation against RAI ablation is based on the fact that no improvement in mortality or morbidity/recurrence has been found in TMC patients. However, the guidelines provide a caveat that patients with PTC and concerning risk factors such as multifocality, lymphadenopathy, or local extension may be considered for RAI ablation. Two large studies have not found any benefit for the use of RAI in TMC patients when multiple foci are present (5, 16). Despite the fact that patients with multifocal disease have consistently been shown to have a higher recurrence rate, RAI was not found to lower the incidence in these studies. In one of the studies, patients receiving RAI were actually found to have a higher rate of recurrence. The retrospective nature of this study leaves open the possibility of an undefined patient selection bias for use of RAI. So, whereas the patient groups appeared similar by comparison, there may have been unaccounted for clinical reasons for some patients receiving RAI, and these patients may have had higher risk of recurrence unrelated to RAI ablation.

In summary, the use of RAI ablation in TMC cases is generally not recommended. Although RAI ablation may improve the usefulness of TG and WBS imaging because it has not been shown to reduce mortality or recurrence in cases of uncomplicated TMC, its use is not advocated. Multifocality and cervical lymphadenopathy are associated with an increased recurrence rate, but it remains unproven that RAI lessens this risk. It is reasonable to use RAI in cases where worrisome features are present and especially in cases with local extension, distant metastasis, or pulmonary involvement.

TSH suppression

Suppression of TSH by means of LT4 therapy has been used in thyroid cancer patients for many years. Data from a meta-analysis supports that TSH suppression is associated with a reduced rate of tumor recurrence (22). The degree of TSH suppression required is related to the stage of disease. Less aggressive TSH suppression is recommended in low-risk thyroid cancer patients (0.1–0.5 mU/liter), whereas more aggressive TSH suppression below 0.1 mU/liter is advocated for patients with stage III or IV disease (23). Also, in cases of low-risk thyroid cancer, the level of TSH suppression may be reduced the longer patients remain disease free. Because suppression of TSH appears to hold some potential negative bone and cardiac consequences, especially when TSH is kept at very low or undetectable ranges, it is preferable to use the least amount of suppression required. Elderly patients; postmenopausal women; patients with coronary artery disease, diabetes mellitus, osteoporosis or osteopenia, or hypertension; and tobacco use may be subject to increased susceptibility to adverse effects from TSH suppression. It has been advocated that TSH suppression should be based on both risk of cancer recurrence/progression and risk to patients from suppressive LT4 therapy (24). Patients with low-risk cancer and low risk from LT4 therapy could have a TSH target between 0.1 and 0.5 mU/liter, whereas those low-risk TMC patients with intermediate or high risk from LT4 would have a TSH goal of 0.5 to 1.0 mU/liter. Once low-risk patients are disease free for 5 to 10 yr, TSH suppression can be lessened potentially to 0.3–2 mU/liter.

Natural history

Patients with TMC have a low recurrence rate, and rarely does the disease impact survival because the mortality rate is low at 0.4–1.0%. It is unclear whether TMC size plays a role in prognosis. Some data indicate a higher recurrence rate associated with lesions larger than 5 mm in comparison to smaller foci (25). However, this association is not a consistent finding (8, 17). Data from Chow *et al.* (9) indicate an expected 10-yr survival of 100%, a locoregional failure-free survival of 92%, and a distant metastasis-free survival of 97%.

Surveillance

Although patients with TMC tend to do well long term, the optimal requirements for disease surveillance are somewhat of a conundrum. Two main follow-up tests, WBS and TG levels, are much more meaningful after RAI ablation. However, as previously mentioned, many patients with TMC will not meet the recommended criteria for ablation. After RAI, stimulated TG levels and WBS can be effectively used for surveillance, whereas these tests are less useful in patients not having undergone RAI ablation. Without preceding ablation, residual uptake on WBS and measurable TG levels can be expected, usually just representing residual normal tissue and not cancer. A little over half of post total/near-total thyroidectomy patients will

have TG levels below 1 ng/ml, whereas the remainder can be expected to have levels above 1 ng/ml with some stimulating up to 25 ng/ml (26). With these limitations on TG and WBS testing, neck ultrasound is a valid option for cancer surveillance in TMC patients. Ultrasound imaging is useful in detecting locoregional disease, with cervical lymph nodes being the most likely form of recurrence in patients with PTC. In low-risk patients, the combination of serum TG and neck ultrasound has been found to have a sensitivity of 96.3% as well as a negative predictive value of 99.5% (27). After thyroidectomy, ultrasound is very sensitive for detecting abnormal lymph nodes and residual masses in the thyroid bed. Lymph nodes with any one or a combination of the following findings are suspicious for cancer: 1) enlarged and rounded in shape; 2) loss of the hyperechoic hilar signal; and 3) vascular flow in the lymph node periphery (28). Fine-needle aspiration of suspicious lymph nodes can be performed to assess for the presence of cancer. Measurement of TG in aspirate washings can enhance the sensitivity for cancer as well (29). However, present-day ultrasound imaging is very sensitive, and during surveillance scanning one can expect to find incidental nonpathological lymph nodes as well. Recent consensus guidelines recommend fine-needle aspiration for lymph nodes with concerning ultrasound characteristics and a size greater than 5–8 mm in the shortest diameter (15).

Monitoring should occur more frequently (every 6–12 months) after the initial diagnosis and can then be spread out at further intervals the longer the patient remains disease free. The extent of testing is somewhat based on the probability of disease being present. The NCCN Practice Guidelines comment that in select low-risk patients, surveillance ultrasound need only be done "if there is a reasonable suspicion for recurrence" (21). However, because recurrences in TMC have been reported as long as 30 yr after initial diagnosis, some form of monitoring should continue long term.

Summary

As a group, patients with TMC have an excellent prognosis. However, a significant number of patients will present with multifocal disease or locoregional lymph node metastasis, both of which are associated with an increase in risk of recurrence. Total thyroidectomy appears of benefit over lesser gland resection (*i.e.* lobectomy, subtotal thyroidectomy), especially in patients with multifocal disease and in those harboring worrisome features. To date, RAI ablation has not been proven beneficial in uncomplicated cases of TMC. No associated reduction in mortality has been noted. The efficacy of RAI in preventing recurrence in patients with multifocal disease is also in question, although ablation can ease follow-up surveillance in such cases. Initial TSH suppression between 0.1 and 0.5 mU/liter is recommended in uncomplicated cases of TMC. As patients remain cancer free, one can consider using a higher TSH goal of 0.3–2 mU/liter. More strict TSH suppression is indicated in patients with distant metastasis or other more aggressive features. Because RAI ablation is frequently not indicated in TMC cases, testing with WBS and TG levels is of limited usefulness secondary to the presence of residual benign tissue. Neck ultrasound can be used as an effective means of surveillance instead. Although TMC patients are at some risk for recurrence, the overall mortality and morbidity is very low in this patient population.

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