HHS Public Access

Author manuscript

Ann Surg Oncol. Author manuscript; available in PMC 2016 May 02.

Published in final edited form as:

Ann Surg Oncol. 2009 November ; 16(11): 3132–3139. doi:10.1245/s10434-009-0647-6.

Papillary Thyroid Microcarcinomas: Big Decisions for a Small Tumor

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Abstract

Background—The clinical significance of papillary thyroid microcarcinoma (PTMC) is debated, and therefore the rise in incidence of PTMC creates management dilemmas. The following study evaluates factors influencing decisions to treat.

Materials and Methods—Between 1994 and 2007, 1361 patients underwent thyroid surgery at a single institution. Of these patients, 107 were diagnosed with PTMC. The type of surgical intervention, likelihood of referral to an endocrinologist, use of radioactive iodine, and administration of suppressive doses of levothyroxine (LT4) were analyzed in relation to patient and tumor characteristics.

Results—Multifocality and larger size were predictive of which patients underwent total thyroidectomy on multivariable logistic regression ($P = .004$ and $P = .001$, respectively). Larger mean tumor size, 0.62 ± 0.004 versus 0.34 ± 0.006 cm, was independently associated with increased likelihood of endocrine referral ($P = .029$). Multifocality, diagnosis via FNA preoperatively, larger mean size of PTMC, and endocrine referral were independently associated with increased likelihood of receiving radioactive iodine (RAI). On multivariable analysis, only total thyroidectomy and endocrine referral were independently associated with treatment with suppressive doses of LT4 ($P = .001$ and .001, respectively). In the 47 patients with unifocal PTMC <0.8 cm diameter, the mean size of tumor focus was larger in the subgroup undergoing total thyroidectomy ($P = .004$). Surprisingly, in these very low risk PTMC patients, the likelihood of RAI for remnant ablation was independently associated with younger patient age ($P = .029$). In the subgroup with unifocal <0.8 cm disease, the mean age of patients receiving RAI was 34 ± 3.3 years versus 48 ± 2.3 years in those not receiving RAI ($P = .003$).

Conclusions—The decision tree in the management of PTMC is beginning at the time of surgery, and referral to endocrinology is associated with a more aggressive course. Younger age is predictive of RAI administration in the lowest-risk PTMC patients.

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The authors have nothing to disclose.

The incidence of papillary thyroid cancer is rising with 49% of the increase because of papillary thyroid microcarcinomas (PTMC).[1] Based on World Health Organization (WHO) criteria, PTMC is a focus of papillary thyroid cancer ≤1 cm diameter.[2] Because physical exam detects 1/3 of nodules seen on ultrasound (US), increased use of imaging modalities has contributed to increased demand for fine needle aspiration of thyroid nodules and subsequently a rise in papillary thyroid cancer >1 cm.[3] However, it is not standard to biopsy lesions less than 1 cm diameter; thus, increased imaging does not directly explain the rise in PTMC.[4] An alternative explanation would be that increased thyroid surgery for benign disease, possibly due to increased detection of thyroid nodules and symptoms at time of FNA, could lead to a rise in incidental PTMC.

It is debated whether PTMC is a normal finding, equivalent to disease, or a precursor of disease. Since the significance of PTMC is unclear, the rise in PTMC incidence creates management dilemmas.

Suggestive that PTMC is a normal finding, on thorough autopsy report more than one-third of individuals have occult PTC with size ranging from 0.15 to 14 mm.[5] In contrast, the incidence of incidental PTMC in patients undergoing thyroid surgery for preoperatively benign disease is 4%–10%.[6,7] The discrepancy in prevalence of PTMC is related to both geographic differences and degree of inspection during pathologic examination.[8,9]

Contrary to the theory that PTMC is a “normal” finding is the theory that PTMC is “cancer” and should be treated as such. There are rare cases of distant metastases and mortality related to PTMC.[10,11] Further supporting the theory that the size cutoff of 1 cm is arbitrary, there are studies showing the likelihood of lymph node involvement is no different in tumors size 8–10 mm vs. 10–15 mm.[12] One would anticipate a “normal” finding to remain in the thyroid and not spread, but metastases to central lymph nodes occur in up to 40% of patients with PTMC.[13,14] In addition, studies show that the likelihood of cancer recurrence is not significantly different among patients with primary tumor size >1 cm versus <1 cm.[15,16]

Suggestive that the clinical significance of PTMC falls between the ambivalence associated with a normal finding and the degree of concern associated with “cancer” is the fact that most patients with PTMC follow an indolent course, and only a few have advanced stage disease.[17] Further implying a gradient of significance, PTMC <5 mm is less likely to have lymph node metastases and cancer recurrence compared with PTMC larger than 8 mm that is associated with more aggressive disease.[6,16]

Although multiple retrospective studies have evaluated the significance of PTMC, the relevance is still debated and the treatment recommendations vague.[4,6,16–18] Given the inconclusive data, it is not clear what is common practice in regard to management of PTMC. In the following study, we retrospectively evaluated factors that influence treatment decisions when a patient is diagnosed with PTMC.

MATERIALS AND METHODS

Between May 1994 and December 2007, 1361 patients underwent thyroid surgery at a single institution. Institutional review board (IRB) approval was obtained to collect deidentified

information on all 1361 patients. Of the 184 patients with a preoperative FNA definitive for cancer, 23 had PTMC based on WHO criteria of tumor size ≤1 cm.[2] Of the 211 patients with follicular neoplasm on preoperative FNA, 9% had incidental PTMC, and 6% of the 886 patients with either benign FNA or no FNA had incidental PTMC ($P = .107$). There were 2 patients who had incomplete preoperative FNA results but were classified as "incidental" PTMC based on clinician notes. Also, 2 patients were excluded from all analysis: 1 patient with a preexisting diagnosis of metastatic follicular thyroid cancer from an outside hospital who had an incidental PTMC found on completion thyroidectomy and another with incomplete medical records from her first surgery at an outside hospital who had PTMC on completion thyroidectomy. These 2 patients were excluded from analysis since their treatment course was determined by their original diagnosis. This left a total of 107 patients with PTMC. Of these 107 patients, 4 were excluded from the analysis when size of primary PTMC was addressed, but they were included in all other analysis. These 4 patients had pathology reports diagnosing PTMC, but there was no comment on exact measurements.

All thyroid surgeries were performed by 4 surgeons, and patients referred to endocrinology were seen by 17 different endocrinologists. Surgery was classified as either total thyroidectomy (bilateral resection including total, near total, or completion thyroidectomy) or unilateral resection (lobectomy with or without isthmusectomy as definitive surgery). Of the benign surgeries, total thyroidectomy was performed when the goiter was compressive, Graves' was the diagnosis, or the contralateral lobe had nodules larger than 1 cm on ultrasound. Only 8 patients underwent completion thyroidectomy after initial lobectomy.

Data were analyzed in relation to tumor size, multifocality, mode of discovery, type of surgery, administration of radioactive iodine (RAI), treatment with levothyroxine (LT4) with goal TSH <0.4 mIU/L, and likelihood of referral to endocrinology. For simple dichotomous data, chi-square was used, and for means ANOVA was used. Because the outcome was binary, multivariable logistic regression analyses was used to identify which factors independently predicted treatment. P values less than .05 were considered significant. Means were reported as mean ± standard error of the mean (SEM). All analyses were performed using SPSS statistical software.

RESULTS

Patient and Tumor Characteristics

Of the 107 patients, 78.5% (84/107) were female and 21.5% (23/107) were male. The mean age was 44 ± 1.31 years. The majority of patients, 84 of 107 (78.5%), had PTMC as an incidental finding on postsurgical pathology report. More than 1/3 of the patients (39/107) had multifocal PTMC as defined by more than 1 PTMC foci. Routine prophylactic central neck dissection was not performed, but 12.1% had lymph nodes that were positive for metastatic PTC. None of the patients had known distant metastases.

In regard to management, total thyroidectomy was performed in 82.2% of patients (88/107). Radioactive iodine was administered to more than half of the patients (57/107), and suppressive doses of LT4 were used to treat 59.8% of patients (64/107) (Table 1).

Although more women were diagnosed with PTMC, the rate of incidental PTMC was nonsignificantly higher in males versus females ($P = .76$). Of the women undergoing surgery for benign disease, including follicular adenoma, 8% (67/835) were diagnosed with incidental PTMC. Similarly, 8.7% of the 196 men undergoing thyroid surgery for benign disease, including follicular adenoma, were diagnosed with incidental PTMC.

Decision for Surgical Resection

Multifocality and larger mean size of primary PTMC were predictive of which patients underwent total thyroidectomy both on multivariable logistic regression ($P = .004$ and $P = .001$, respectively). Of patients with more than 1 tumor focus 97% (38/39) underwent total thyroidectomy versus 74% (50/68) of those with only 1 tumor focus. Mean cancer size was 0.61 ± 0.004 cm in patients who underwent total thyroidectomy versus 0.22 ± 0.004 cm in those who underwent lobectomy. Of patients with a tumor ≥0.8 cm, 100% (27/27) underwent total thyroidectomy. Of patients with tumor ≥0.5 cm 97% (56/58) underwent total thyroidectomy (including the patients with primary tumor size ≥0.8 cm), while 67% (30/45) of those with tumor size <0.5 cm underwent total thyroidectomy.

When PTMC was discovered via preoperative analysis, whether it be FNA of a lymph node, a portion of a large nodule, or a suspicious small nodule, 96% (22/23) of patients with PTC diagnoses preoperatively underwent total thyroidectomy versus 79% (66/84) of those diagnosed by surgical pathology. However, on multivariable analysis, preoperative diagnosis was not an independent predictor of degree of surgical resection ($P = .875$) (Table 2).

Prophylactic central neck dissection is not routine at this institution, and therefore the true number of positive lymph nodes is unknown. However, 13 of 107 patients (12%) had positive lymph nodes resected surgically. All 13 patients underwent total thyroidectomy, and 12 of 13 were referred to endocrinology. Of the patients with positive lymph nodes, 10 of 13 (77%) received both RAI and suppressive doses of LT4.

Decision for Referral to Endocrinology

The same variables that predict likelihood of total thyroidectomy versus unilateral resection play a role in determining which patients are referred to endocrinologist. Tumor size was an independent predictor of endocrine referral ($P = .029$) and multifocality showed a trend for referral ($P = .054$) (Table 3).

Decision for Radioactive Iodine as Remnant Ablation

Multifocality, diagnosis via FNA preoperatively, larger mean size of PTMC, and endocrine referral were independently associated with increased likelihood of receiving RAI on multivariable analysis ($P = .035$, .048, .044, and .01, respectively). Although all variables (multifocality, method of discovery, mean tumor size, total thyroidectomy, and endocrine referral) were associated with RAI administration on univariate analysis, surgical choice was no longer predictive on multivariable logistic regression analysis (Table 4). Interestingly, the mean age of patients receiving RAI was younger than those not receiving RAI ($P = .015$). Patients receiving RAI had a mean age of 41 ± 1.8 years versus those not receiving RAI had a mean age of 48 ± 1.8 years.

Decision for Suppressive Doses of Levothyroxine

On univariate analysis, multifocality, larger mean size of primary PTMC, total thyroidectomy, and endocrine referral were associated with treatment with suppressive doses of LT4. However, on multivariable analysis, only total thyroidectomy and endocrine referral were independently associated with likelihood of treatment with suppressive doses of LT4 (P = .001 and .001, respectively) (Table 5).

Management of the Lowest Risk PTMC

Since multifocality and size ≥0.8 cm may be associated with worse prognosis and thus may warrant more aggressive management, these patients were excluded from the following analysis with the goal of analyzing the lowest-risk PTMC patients.[4,6,12] The lowest risk PTMC patients consisted of 47 patients with unifocal PTMC <0.8 cm diameter. Multivariable analysis was performed to determine which patient or tumor characteristics predicted more aggressive treatment. Larger mean size of primary PTMC was the only independent predictor of total thyroidectomy over unilateral resection. The mean size of PTMC undergoing total thyroidectomy was 0.41 ± 0.004 cm and the mean size of PTMC undergoing unilateral resection was 0.23 ± 0.004 cm (multivariable P = .004). There was no one variable that was independently associated with likelihood of referral to endocrinology. Surprisingly, the only variable independently associated with RAI administration was younger patient age (P = .029) (Table 6). Multifocality, method of discovery, tumor size, endocrine referral, and surgery were no longer independent predictors on multivariable analysis. The mean age of patients with lowest risk PTMC receiving RAI was 34 ± 3.3 years, and the mean age of patients not receiving RAI was 48 ± 2.3 years (P = .003). Similar to the entire group of PTMC patients, total thyroidectomy and endocrine referral were associated with suppressive doses of LT4 (P = .001 and .002, respectively).

DISCUSSION

The clinical significance of papillary thyroid microcarcinoma (PTMC) is debated, and management reflects this conflict. On one hand, the TNM classification system does not address PTMC as a separate tumor. PTMC is included in the T1 category, which has tumors as large as 2 cm.[19] This indirectly suggests prognosis and management is the same for all T1 tumors. Yet, recent ATA guidelines suggest unilateral resection alone is adequate in patients with <1 cm, intrathyroidal, node negative, low-risk tumors, and radioactive iodine is primarily recommended for PTMC patients with multifocality, nodal involvement, extrathyroidal extension, or aggressive histology.[4]

In addition to debates on clinical significance, the management of PTMC is further complicated by the likelihood of selection bias influencing both diagnosis and subsequently treatment. Extent of pathology exam is closely related to the likelihood of PTMC diagnosis.[5,8,9] For example, although it was only a trend, in our patient population there was increased detection of PTMC in patients undergoing surgery for follicular neoplasms versus benign disease (9% vs. 6%, respectively). An increased number of slices are made by pathology when attempting to determine follicular carcinoma versus follicular adenoma.

Although the primary tumor may be deemed follicular adenoma, more meticulous inspection leads to detection of incidental PTMC.

In addition, in our patient population the high rate of female patients versus male patients with PTMC is likely due to selection bias. Although the absolute number of PTMC diagnoses was higher in women, the incidence rate in males versus females was similar (8.7% vs. 8.0%). Previous studies have also shown the sex distribution is essentially equal for PTMC.[5,8] However, since women are more likely to undergo thyroid surgery for benign reasons, they have an increased detection rate of PTMC.

Given the inconsistency in likelihood of diagnosis and the ongoing debate on clinical significance, we analyzed the management of PTMC at a single institution to determine which variables predicted clinical management.

In our patient population, total thyroidectomy was performed on 82% of patients with PTMC (88/107). One reason a surgeon may favor total thyroidectomy for PTMC is out of concern for multifocality. Multifocality is common with PTC, and the likelihood of diagnosis is dependent on degree of inspection.[13] If both lobes are not examined, the diagnosis of multifocality may be missed. Previous studies have shown multifocality is not caused by metastases from a single focus but rather a predisposition of some thyroids to develop cancer.[20] Multifocality is associated with increased cancer recurrence, and studies have shown that there is no difference in rate of contralateral disease in patients with tumors >1 cm vs. ≤1 cm.[14,21] Despite this concern for multifocality, data from the National Cancer Database have shown that there is no survival or recurrence difference in patients with tumors <1 cm who undergo unilateral resection versus total thyroidectomy.[18] Thus, in unilateral PTMC without high-risk features, lobectomy alone is likely adequate.

A second reason for considering total thyroidectomy over lobectomy is the reported low frequency of permanent recurrent laryngeal nerve damage or permanent hypocalcemia with experienced, specialized surgeons.[22] The complication rates in this series were relatively low with 2 patients (1.8%) experiencing transient hypoparathyroidism, 1 patient (0.9%) experiencing permanent hypoparathyroidism, and 1 patient (0.9%) experiencing transient postoperative hoarseness.

On multivariable analysis, the surgeons at our institution were more likely to perform total thyroidectomy if there was more than 1 tumor foci and if the mean size of the primary PTMC was larger. These management decisions seem consistent with data showing increased cancer recurrence in multifocal disease and higher likelihood of lymph node involvement in PTMC closer to 1 cm.[6,12,14]

A little over three-fourths (83/107) of patients diagnosed with PTMC were referred to endocrinology. Of note, mean tumor size was the only variable predictive of endocrine referral. Just seeing an endocrinologist was independently associated with increased likelihood of RAI for remnant ablation and for treatment with suppressive doses of LT4.

The utility of RAI for PTMC is not clear.[23] It is probable that it can be avoided in patients with unifocal PTMC without tumor extension or lymph node involvement.[4,8] However,

53.3% (57/107) of patients with PTMC received RAI, and this exceeds the number with multifocal disease or high-risk features. In addition to endocrine referral, multifocality, larger mean size of PTMC, and detection prior to surgery were also associated with increased likelihood of RAI. The use of suppressive doses of LT4 did not correlate 1 to 1 with the use of RAI.

Similar to treatment with RAI, type of surgery and referral to an endocrinologist increased the likelihood of therapy with suppressive doses of LT4. Total thyroidectomy, remnant ablation with RAI, and suppressive doses of LT4 are considered standard of care for thyroid cancer. Suppressive doses of LT4 improve outcome in high-risk patients, and modest TSH suppression improves outcome in moderate-risk patients, but low-risk thyroid cancer patients have an excellent prognosis regardless of intervention.[24] Since the majority of patients with PTMC are very low risk, the benefit of suppressive doses of LT4 is questionable.

Because multifocal PTMC and PTMC with tumor size ≥0.8 cm may be associated with a more aggressive course, these patients were later excluded from the analysis.[4,6,12,13] This left 47 patients with isolated <0.8 cm PTMC. Multivariable analysis revealed that within this group, larger mean size of primary PTMC was associated with increased likelihood of total thyroidectomy. The mean size of tumor focus was 0.41 ± 0.004 cm in patients undergoing total thyroidectomy and 0.23 ± 0.004 cm in those undergoing unilateral resection. No one variable had an independent association with likelihood of referral to endocrinology. Interestingly, younger patient age was the only independent predictor of RAI administration on multivariable logistic regression. The benefits of RAI include potential reduction of lymph node recurrence and ease of using post-treatment thyroglobulin as a tumor marker.[25] However, RAI is not without risks; a recent analysis of 30,278 patients treated for thyroid cancer found the risk of nonthyroid second primary cancer is higher in those patients treated with radioactive iodine.[26] Of those patients treated with RAI, younger patients had the highest risk of a second primary cancer.[26] In our series, it is not clear if the association between younger patient age and RAI administration is due to patient preference or endocrinology recommendation. However, patients under age 45 with unifocal PTMC have an excellent prognosis, and the benefits of RAI for remnant ablation may not exceed the risks in this subgroup.[4,25]

Similar to the assessment of suppressive doses of LT4 in all PTMC patients, type of surgery and endocrine referral were independently associated with increased likelihood of treatment with suppressive doses of LT4 in patients with unifocal <0.8 cm tumor.

A major limitation of this current study is the fact that all patients came from a single institution. A second limitation of this study is the fact that no information was gathered on the role of patient preference in treatment course, and this may play a more prominent role than expected. Despite these limitations, this study has several strengths. Because it is a single-institution study instead of pooled data from a national registry, there is information on method of discovery, specific tumor size, and multifocality. Inclusion of these details is necessary to illustrate the management course in the lowest risk tumors. In addition, since there is no protocol for PTMC at this institution, the involvement of 17 different

endocrinologists suggest the pattern of care may be more similar to the variation seen in communities at large versus a consistent pattern representative of one institution with an institutional protocol.

In conclusion, PTMC is a diagnosis closely linked to degree of inspection. Therefore, diagnosis and subsequent treatment course is plagued with selection bias. Treatment recommendations vary because although typically indolent, there are examples of aggressive PTMC. In the current study, we do not attempt to assess optimal management, but rather to evaluate the current management of PTMC in an academic center. An effort was made to identify which clinical and pathologic features are being used to determine treatment. Our study illustrates that the management of PTMC starts at the time of surgery as 78.5% of PTMC are incidental postoperative findings. Similar to compiled data, we also found a pattern of more aggressive management of PTMC than what is advocated by scientific societies such as the American Thyroid Association.[4,27] Of particular concern, we found younger patient age was associated with RAI administration in all PTMC patients and perhaps most concerning, associated with RAI administration in our lowest-risk PTMC patients. Further investigation of this association is warranted.

ACKNOWLEDGMENT

The Academic Oncologist K12 Training Grant through the University of Wisconsin Paul P. Carbone Comprehensive Cancer Center supports Megan R. Haymart's research, CA K12 087718. Herb Chen is funded by NIH NCI-RO1CA109053 and NIH NCI-R01CA121115. We thank Jesse Quinn and Ben Hofeld for their role in data collection.

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TABLE 1

Patient and tumor characteristics

	***N* = 107**
Mean age	44 ± 1.31 years
Gender	
Male	23 (21.5%)
Female	84 (78.5%)
Surgery	
Total thyroidectomy	88 (82.2%)
Unilateral resection	19 (17.8%)
RAI	57 (53.3%)
Suppressive LT4	64 (59.8%)
Referral to endo	83 (77.6%)
Discovered	
FNA	23 (21.5%)
Incidental	84 (78.5%)
Multifocal	39 (36.4%)
Lymph Nodes	13 (12.1%)
Distant Metastasis	0 (0%)

TABLE 2

Decision for surgical resection

	Total thyroidectomy	Unilateral resection	*P* value	Multivariable *P* value
Foci				
1	50/68 (74%)	18/68 (26%)	.001	.004
>1	38/39 (97%)	01/39 (3%)		
Discovered				
FNA	22/23 (96%)	1/23 (4%)	.046	.875
Incidental	66/84 (79%)	18/84 (21%)		
Mean size (cm)	0.61 ± 0.004	0.22 ± 0.004	.001	.001
Larger size (cm)				
≥0.8	27/27 (100%)	0/27 (0%)	.003	
<0.8	59/76 (78%)	17/76 (22%)		
Smaller size (cm)				
≥0.5	56/58 (97%)	2/58 (3%)	.001	
<0.5	30/45 (67%)	15/45 (33%)		

TABLE 3

Decision to refer to endocrinology

	Endocrine	No endocrine	*P* value	Multivariable *P* value
Foci				
1	48/68 (71%)	20/68 (29%)	.018	.054
>1	35/39 (90%)	4/39 (10%)		
Discovered				
FNA	22/23 (96%)	1/23 (4%)	.013	.208
Incidental	61/84 (73%)	23/84 (27%)		
Mean size (cm)	0.62 ± 0.004	0.34 ± 0.006	.001	.029
Surgery				
Total thyroidectomy	74/88 (84%)	14/88 (16%)	.001	.42
Unilateral resection	9/19 (47%)	10/19 (53%)		

TABLE 4

Decision for radioactive iodine as remnant ablation

	RAI	No RAI	*P* value	Multivariable *P* value
Foci				
1	28/68 (41%)	40/68 (59%)	.001	.035
>1	29/39 (74%)	10/39 (26%)		
Discovered				
FNA	21/23 (91%)	2/23 (9%)	.001	.048
Incidental	36/84 (43%)	48/84 (57%)		
Mean size (cm)	0.71 ± 0.004	0.35 ± 0.004	.001	.044
Surgery				
Total thyroidectomy	57/88 (65%)	31/88 (35%)	.001	.796
Unilateral resection	0/19 (0%)	19/19 (100%)		
Referral to endo				
Yes	56/83 (67%)	27/83 (33%)	.001	.01
No	1/24 (4%)	23/24 (96%)		

TABLE 5

Decision for suppressive dose of levothyroxine (LT4): Goal TSH <0.4 mIU/L

	Suppressive LT4	Nonsuppressive LT4	*P* value	Multivariable *P* value
Foci				
1	35/61 (51%)	33/68 (49%)	.016	.934
>1	29/39 (74%)	10/39 (26%)		
Discovered				
FNA	16/23 (70%)	7/23 (30%)	.202	.461
Incidental	48/84 (57%)	36/84 (43%)		
Mean Size (cm)	0.61 ± 0.004	0.45 ± 0.005	.019	.4
Surgery				
Total thyroidectomy	62/88 (70%)	26/88 (30%)	.001	.001
Unilateral resection	2/19 (11%)	17/19 (11%)		
Referral to endo				
Yes	61/83 (73%)	22/83 (27%)	.001	.001
No	3/24 (12%)	21/24 (88%)		

TABLE 6

Multivariate of lowest-risk PTMC: excluding PTMC with multifocality or size 0.8 cm or greater ($N = 47$)

Management		***P* value**
Surgery = total Thyroidectomy	Independently related to size of dominant nodule	.004
Endocrine referral	No dependence on any one variable	NA
RAI	Independently related to younger age	.029
	Mean age + RAI = 34 ± 3.9 years and mean age − RAI = 48 ± 2.3 years	
Suppressive LT4	Independently related to total thyroidectomy and endocrine referral	.001, .002