Patients with Multifocal Macroscopic Papillary Thyroid Carcinoma Have a Low Risk of Recurrence at Early Follow-Up after Total Thyroidectomy and Radioactive Iodine Treatment

Amanda La Greca^a Bin Xu^b Ronald Ghossein^b R. Michael Tuttle^a
Mona M. Sabra^a

^aEndocrinology Service, Department of Medicine, and ^bDepartment of Pathology, Memorial Sloan-Kettering Cancer Center and Weill-Cornell College of Medicine, New York, N.Y., USA

Key Words

Thyroid cancer recurrence · Multifocal macroscopic papillary thyroid cancer · Clinical outcomes

Abstract

Background: Multifocal thyroid cancer involvement is a common presentation in papillary thyroid cancer. The risk of recurrence of intrathyroidal multifocal papillary microcarcinoma (<1 cm) is documented to be low. However, the risk of recurrence of multifocal macroscopic thyroid cancer is not known. Prior studies have suggested that both the number of foci and the presence of nodal involvement at diagnosis are important predictors of recurrence in multifocal papillary thyroid carcinoma (PTC). **Objectives:** In this retrospective review of 99 patients presenting with multifocal macroscopic PTC (with 2 tumor foci >1 cm) without gross extrathyroidal extension, we examined the clinical outcomes of patients in the first 2 years after the initial therapy and at the end of the follow-up period (median: 5 years). **Results:** Half of the patients presenting with multifocal macroscopic PTC had nodal involvement at diagnosis. Only 4 patients had a recurrence

on long-term follow-up, all with classic or tall-cell variant PTC with bulky nodal involvement at diagnosis. The number of tumor foci did not influence the risk of recurrence in this cohort. The median time to recurrence in these 4 patients was 11 years, with all patients having a recurrence after 9 years of follow-up. None of patients developed distant metastasis or died from thyroid cancer. **Conclusions:** Patients presenting with multifocal macroscopic papillary thyroid cancer without bulky nodal involvement or gross extrathyroidal extension have a low risk of thyroid cancer recurrence.

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Introduction

Multifocal involvement of the thyroid gland is a well-recognized feature of papillary carcinoma. The reported frequency is about 20%, with wide variations depending on the extent of the sampling and reporting by the pa-

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thologist [1–3]. Multifocal papillary thyroid carcinomas (PTC) can be divided into 2 categories depending on the tumor size: multifocal papillary microcarcinoma (all of the lesions sized <1 cm) and multifocal macroscopic papillary thyroid cancer (includes more than 1 tumor focus sized ≥ 1 cm).

Several studies have confirmed the risk of structural disease recurrence in multifocal papillary microcarcinoma treated with total thyroidectomy to be low, varying from 4 to 6% [4–6]. In similar patients, Baudin et al. [7] demonstrated that the number of histologic foci and the extent of surgery significantly influenced the risk of recurrence in multivariate analysis. As such, the recurrence rate for patients with unifocal thyroid microcarcinoma was 1.2% compared to 8.6% for patients with multifocal thyroid microcarcinoma ($p = 0.002$) [7]. Other large retrospective studies have failed to demonstrate that multifocality is a risk factor for thyroid cancer recurrence [8, 9].

Given the calculated low risk of recurrence of multifocal papillary thyroid microcarcinoma after total thyroidectomy, routine radioactive iodine (RAI) ablation is not recommended and close surveillance is advocated [10]. In the updated 2015 American Thyroid Association guidelines, the 3-tiered categorical system (i.e. low, intermediate, and high risk of recurrence) did not specifically address the outcomes of and management approach for patients presenting with multifocal macroscopic papillary thyroid cancer [10]. In the absence of studies estimating the risk of structural recurrence in these patients, the treating physician often errs on the side of caution, electing to administer RAI ablation to patients presenting with multifocal macroscopic papillary thyroid cancer and thus potentially providing unnecessary treatment and potentially increasing the risk of treatment-related morbidity.

In this study, we investigated the risk of structural disease recurrence in patients with multifocal macroscopic papillary carcinoma as an independent (prognostic) factor. We hypothesized that the risk of recurrence of multifocal macroscopic papillary thyroid cancer in the absence of other aggressive features, such as gross extrathyroidal extension and bulky nodal involvement, is low and that routine RAI therapy is not required when treating these patients. Our primary end point was the presence of persistent/recurrent structural disease after the initial therapy and at the final follow-up in patients with multifocal PTC with at least 2 tumors, all with a longest diameter of at least 1 cm.

Materials and Methods

Patient Selection

After obtaining institutional review board approval, we reviewed the electronic medical records of 124 subjects with multicentric thyroid carcinoma treated at the Memorial Sloan-Kettering Cancer Center between 1985 and 2002 and 2008 and 2015. Accurate determination of multifocality on pathologic examination was not systematically collected at our center for patients diagnosed between 2002 and 2008. These patients were not included in the analysis. Patients were included if they met all of the following conditions: (1) was treated with at least a total thyroidectomy with or without lymph node dissection, (2) had a diagnosis of PTC on surgical pathology, (3) had 2 or more thyroid cancer foci greater than 1 cm in longest diameter; (4) had at least a 6-month follow-up after surgery, (5) had appropriate follow-up with unstimulated thyroglobulin (Tg) and Tg antibodies (TgAb) and imaging (neck ultrasound, CT/MRI, and RAI scanning).

The exclusion criteria were: (1) patients with follicular, Hürthle cell, poorly differentiated, medullary or anaplastic thyroid cancer; (2) patients undergoing lobectomy alone; (3) patients with gross extrathyroidal extension on the surgical specimen; (4) patients without appropriate follow-up, and (5) patients with chronic TSH elevation. From 124 potential patients, 99 patients were selected for this study.

Histopathologic Analysis

Tumors were classified according to the latest World Health Organization criteria, with the exception of tall-cell variant (TCV) PTC [11]. Tumors were classified as TCV PTC if they contained >50% tall cells. The latter cell type was defined as having a height at least twice its width, with oncocytic cytoplasm [12]. All cases were diagnosed by subspecialized head and neck pathologists with expertise in thyroid neoplasia.

Patient Follow-Up

Patients were followed every 6 months during the first year and then at 6- to 12-month intervals thereafter at the discretion of the treating physician. The frequency of the follow-up visits was based on the estimated risk of recurrence for each individual patient and the clinical course of the disease.

Clinical End Points

Each patient was risk stratified according to the seventh edition of the American Joint Committee on Cancer TNM (AJCC/TNM) staging system (stage I, II, III, or IV) and the American Thyroid Association (ATA) risk of recurrence stratification system (low, intermediate, or high) [10, 13]. Clinical outcomes were then assessed at 2 time intervals: best response to the initial therapy and status at the final follow-up. The best clinical response to the initial therapy was assessed based on clinical data obtained in the first 2 years of follow-up using a restratification model proposed and validated by our group [14, 15]. The definitions of clinical response varied depending on whether the patient was treated with RAI ablation or not. Specifically, patients who received a total thyroidectomy and RAI ablation were classified as having: (1) an excellent response if they achieved a nonstimulated Tg level <0.2 ng/ml or undetectable TgAb and negative imaging (normal neck ultrasound and/or cross-sectional imaging such as CT or MRI and RAI scanning), (2) an indeterminate response if they achieved an unstimulated Tg level between 0.2 and 1 ng/ml or TgAb levels were stable

or declining (in the absence of structural or functional disease) or had nonspecific findings on imaging studies or a faint uptake in the thyroid bed on RAI scanning, (3) a biochemical incomplete response if they achieved a nonstimulated Tg level >1 ng/ml or increasing TgAb levels and nonsuspicious imaging findings, or (4) a structural incomplete response if they had structural evidence of disease regardless of Tg or TgAb levels. Patients who received a total thyroidectomy without RAI ablation were classified as having: (1) an excellent response if they achieved a nonstimulated Tg level <0.2 ng/ml or undetectable TgAb and negative imaging (normal neck ultrasound and/or cross-sectional imaging such as CT or MRI and RAI scanning), (2) an indeterminate response if they achieved a nonstimulated Tg level between 0.2 and 5 ng/ml or TgAb levels were stable or declining (in the absence of structural or functional disease) or they had nonspecific findings on imaging studies or a faint uptake in the thyroid bed on RAI scanning, (3) a biochemical incomplete response if they achieved a nonstimulated Tg level >5 ng/ml or increasing Tg values over time with similar TSH levels or increasing TgAb levels and negative imaging, or (4) a structural incomplete response if there was structural or functional evidence of disease regardless of the Tg or TgAb levels [15].

The clinical status at the time of the last follow-up evaluation was recorded for each patient [no clinical evidence of disease, indeterminate response (using the same criteria as above), biochemical persistent disease, structural persistent disease, recurrent disease, or thyroid-related death]. 'No evidence of disease' referred to patients without biochemical or structural evidence of disease. None of the patients had persistent elevated Tg or rising antithyroglobulin antibodies without a structural correlate (biochemical persistent disease). In all of the patients who had a recurrence, the site of recurrence was the neck, and none of the patients developed distant metastasis. The Tg cutoffs used to assess the final clinical status were similar to those used for the initial response to therapy.

Laboratory Studies

Between 1990 and 1997, various Tg assays with functional sensitivities of approximately 1 mg/ml were used. Starting in 1998, all Tg values were measured using the DYNOfest-TgS immunoradiometric assay (Brahms Inc., Berlin, Germany; functional sensitivity: 0.6 ng/ml normalized to Certified Reference Material 457) [16]. TgAb levels were measured using a Siemens Immulite 2500 Chemistry Analyzer (Siemens Healthcare Diagnostics Inc., Deerfield, Ill., USA). Given the variability of Tg assay detection levels over time, we generally assumed that an excellent response was achieved if the stimulated Tg level was <1 ng/ml with undetectable anti-Tg antibodies. If this was not available, we considered a nonstimulated Tg level below the detection level of that specific assay as enough indication of an excellent response. Using this definition, we recognize that a few patients diagnosed before 1998 may have been misclassified as having an excellent response to the initial therapy rather than an indeterminate response.

Statistical Methods

Continuous data are presented as means $\pm$ SD or medians (range), as appropriate for each variable. Analyses were performed using SPSS software (version 24; SPSS, Inc., Chicago, Ill., USA).

The primary end point was the presence of persistent/recurrent structural disease after the initial therapy and at the final follow-up in patients with multicentric PTC when at least 2 foci measured 1 cm or more in longest diameter.

Results

Clinicopathologic Characteristics of the Cohort

The clinicopathologic characteristics of the 99 patients included in this analysis are summarized in table 1. The patients were a median of 47 years old at the time of the cancer diagnosis, and they had a median of 2 additional foci of thyroid cancer. The median size was 2 cm for the largest tumor and 1.3 cm for the second biggest tumor. Classic PTC was the histology of the largest tumor in more than half of the sample (55%), followed by tall cell (31%) and follicular variant (13%). The histology of the second biggest focus was more likely to be similar to that of the primary tumor in classic and follicular variant PTC but not in TCV PTC. Thus, the concordance in histology between the largest and second biggest tumors was 63% in classic PTC, 50% in follicular variant PTC, and 19% in TCV PTC. Twenty-eight percent of the largest tumors were totally encapsulated and 17% displayed vascular invasion.

All of the patients were treated with a total thyroidectomy. Neck dissection, either central or lateral, was performed only if suspicious nodes were detected by imaging ahead of the surgery and intraoperatively. Thus, none of the studied patients had a prophylactic neck dissection. Half of the patients with multifocal macroscopic PTC had nodal involvement (55%), with 45 patients with N1a disease (median: 3 affected nodes) and 38 patients with N1b disease (median: 4 affected nodes). The median size of the largest metastatic node was 1.4 cm, and extranodal extension was observed in 20% of the affected nodes.

Five patients were found to have metastasis to the lungs at the time of the cancer diagnosis. Those patients were more likely to be women (80%) with a median age of 38 years, with larger primary tumors (median size: 3.5 cm) and significant nodal disease in the central (5 patients, median: 3 affected nodes) and/or lateral compartments (4 patients, median: 9 affected nodes) with extranodal extension (seen in 4 patients). All of these patients had lung micrometastasis (lung nodules <1 cm). Two were detected on diagnostic radioiodine scan at the initial therapy, and 3 were detected by a posttherapy scan and confirmed with a CT scan. At the final follow-up, 4 patients had persistent stable structural disease and 1 patient had no evidence of disease. None of the patients developed distant metastasis during the course of the follow-up.

The majority of the patients received RAI ablation ($n = 74$; 75%), with a median activity of 145 mCi. The administered activity was not known in 5 of these patients. Nine patients received more than one RAI activity during

Table 1. Clinical characteristics of the cohort (n = 103)

Characteristics	Value	Characteristics	Value
Age at diagnosis, years		Size of the second biggest tumor ^a , cm	
Mean ± SD	47.7 ± 14.8	Mean ± SD	1.6 ± 0.8
Median	47	Median	1.3
Range	14–81	Range	1.0–5.2
Female gender	71 (69)	Patients with N1a affected nodes ^b	52 (69)
Histology of the largest primary tumor		Metastatic N1a nodes, n	
Classic PTC	57 (55)	Mean ± SD	4.8 ± 4.5
Follicular variant PTC	14 (14)	Median	3
TCV PTC	32 (31)	Range	1–18
Size of the primary tumor, cm		Patients with N1b affected nodes ^c	36 (92)
Mean ± SD	2.55 ± 1.58	Metastatic N1b nodes, n	
Median	2.0	Mean ± SD	8.8 ± 9.9
Range	1.0–9.2	Median	6
Thyroid cancer stage at diagnosis		Range	1–41
I	47 (46)	Size of the largest metastatic node ^d , cm	
II	11 (11)	Mean ± SD	1.6 ± 1.1
III	28 (27)	Median	1.3
IV	17 (16)	Range	0.1–4.0
Extrathyroidal extension		Presence of extranodal extension ^e	22 (21)
None	47 (46)	Other metastatic sites	
Minimal	56 (54)	Lungs	6 (6)
Vascular invasion		Modified 2009 ATA risk stratification, %	
None	85 (83)	Low	34
Present	18 (17)	Intermediate	46
Tumor encapsulation		High	20
None	36 (35)	RAI therapy	74 (72)
Present	29 (28)	First RAI therapy activity, mCi ^e	
Partial	38 (37)	Mean ± SD	131 ± 66
Tumor at the surgical margin	20 (19)	Median	145
Additional foci in the thyroid ^a , n		Range	30–373
Mean ± SD	3.4 ± 3.3	Cumulative dose in patients with additional	
Median	2	RAI activities ^f , mCi	
Range	1–20	Mean ± SD	399 ± 195
Histology of the second biggest focus		Median	380
Classic PTC	57 (55)	Range	225–865
Follicular variant PTC	38 (37)		
TCV PTC	8 (8)		

Values are presented as numbers (%) unless otherwise stated. ^a n = 92. ^b n = 75. ^c n = 39. ^d n = 57; 5 patients had an unknown initial dose. ^e n = 43. ^f n = 69.

the course of their follow-up (7%), and the median cumulative activity for these 9 patients was 380 mCi (mean: 399 ± 195, range 225–865).

The patients were followed for a median of 3 years (range 0.12–29.2). After excluding for patients with gross extrathyroidal extension at the time of thyroid cancer diagnosis, none of the patients with multifocal macroscopic thyroid cancer developed distant metastasis on follow-up or succumbed to their disease.

Clinical Outcomes

The clinical outcomes of the patient cohort are summarized in figure 1. Of the 99 patients included in the final analysis, 5 had recurrences of thyroid cancer. All 5 patients had nodal involvement at diagnosis and none had distant metastasis at diagnosis or during the course of their follow-up. Thus, all recurrences were in the neck. The clinical characteristics and outcomes of these patients are summarized below.

Fig. 1. Clinical outcomes of treated patients with multifocal macroscopic thyroid cancer. NED = No evidence of disease.

Clinical Response Based on the Initial ATA Risk Stratification

Using the 2009 Modified ATA risk classifier, 34% of the patients were classified as low risk, 46% as intermediate risk, and 19% as high risk. In the first 2 years after the initial therapy, 37% achieved an excellent response, 45% achieved an indeterminate response, 7% achieved a biochemical incomplete response, and 8% had a structural incomplete response. At the end of the follow-up period (median: 3 years), 60% of the patients had no evidence of disease, 7% of the patients had persistent disease, and only 1 patient (1%) had recurrent disease (table 2). A third of the patients had an indeterminate response with undetectable Tg levels and/or detectable but decreasing anti-thyroglobulin antibodies and/or stable nonspecific thyroid bed or lung nodules.

Interestingly, none of the 34 patients with ATA low-risk thyroid cancer had long-term recurrences of thyroid cancer. Two of the 19 patients with ATA high-risk thyroid cancer at diagnosis had a recurrence, and 2 of the 46 patients with an ATA intermediate risk at diagnosis had

a long-term recurrence of thyroid cancer. All of the patients who had a recurrence had nodal involvement at diagnosis.

A total of 74 patients had follow-up over 1 year. Their risk stratification and outcomes are summarized in table 3. Five patients (6%) had a recurrence during disease follow-up, with almost all recurrences occurring 5 years or later after the thyroid cancer diagnosis. At the final follow-up (median: 5 years), similarly to the overall cohort, more than half of the patients had no evidence of disease (55%), 10% had persistent stable disease, 34% had achieved an indeterminate response, and 1 patient had recurrent disease.

Outcomes of Patients Who Received RAI Ablation Compared to Those Who Did Not

Seventy-four patients received RAI ablation. Five of these patients had a recurrence on follow-up. The clinical characteristics of these 5 patients are summarized below. Seven of the 74 patients who received RAI ablations were treated with additional RAI therapies; in the

Table 2. Clinical outcomes of all of the patients (n = 103)

Time from diagnosis to the last follow-up, years	
Mean ± SD	5.7 ± 6.0
Median	3.2
Range	0.3–29.1
Best response to the initial therapy ^a	
Excellent	44 (38)
Biochemical incomplete	7 (7)
Structural incomplete	8 (8)
Indeterminate	45 (47)
Recurrence during the course of follow-up	5 (5)
Clinical outcomes at the end of follow-up ^b	
No evidence of disease	61 (61)
Structurally persistent disease	6 (6)
Recurrent disease (neck)	1 (1)
Indeterminate	31 (31)
No thyroid cancer-related death ^b	99 (100)

Values are presented as numbers (%) unless otherwise stated.
^a n = 97. ^b n = 99.

first 2 years after the initial therapy, 1 had an excellent response, 1 achieved an indeterminate response, 1 achieved a biochemical incomplete response, and 4 had a structural incomplete response. At the end of the follow-up and with interim repeat RAI therapy, 2 had no evidence of disease, 2 achieved an indeterminate response, and 3 had stable persistent thyroid cancer. None of these 7 patients had neck recurrences or developed metastasis on follow-up.

At the discretion of the treating physician, 25 patients were initially treated with active surveillance without RAI ablation after the initial surgery. Only 3 of these patients had N1 disease, with up to 3 affected nodes measuring up to 6 mm. Four of these 25 patients were subsequently treated with RAI with a median activity of 92 mCi (mean: 102 ± 34 mCi, range 75–150). None of these patients had a recurrence during the course of their follow-up. Eighteen of these 25 patients had no evidence of disease, while 7 achieved an indeterminate response.

Clinical Characteristics of the Patients with Recurrences

Tables 4 and 5 describe the clinical characteristics of the 5 patients who had a recurrence during the course of follow-up. All of the patients received an initial RAI ablation. The median size of the primary tumor was 2.7 cm; focal vascular invasion (<4 invasive foci) was only noted

Table 3. Clinical outcomes including patients with follow-up of more than 1 year (n = 79)

Time from diagnosis to the last follow-up, years	
Mean ± SD	7.3 ± 6.4
Median	5.0
Range	1.0–29.2
Modified 2009 ATA risk stratification	
Low	22 (28)
Intermediate	36 (46)
High	21 (26)
Best response to the initial therapy	
Excellent	33 (42)
Biochemical incomplete	8 (10)
Structural incomplete	10 (13)
Indeterminate	28 (35)
Recurrence during the course of follow-up	5 (6)
Clinical outcomes at end of follow-up	
No evidence of disease	68 (86)
Persistent disease	10 (13)
Recurrent disease (neck)	1 (1)
Thyroid cancer-related death	3 (4)

Values are presented as numbers (%) unless otherwise stated.

in 1 case, and 3 cases had minor extrathyroidal extension and only 1 case had positive margins on surgical resection. The median size of the separate foci was 1.3 cm. Four out of 5 patients had bulky nodal involvement in the lateral neck with extranodal extension at diagnosis.

The best response to the initial therapy in those 5 patients was excellent (n = 1), biochemical incomplete (n = 3), and indeterminate (n = 1). One patient with an initial biochemical incomplete response presented with structural recurrence 2 years after the initial diagnosis. Four patients had a long-term recurrence. The median follow-up of the patients who had a recurrence was 15 years, and the median time to recurrence was 11 years. In all patients, the recurrence occurred in the neck; all but 1 patient had a recurrence after 9 years of follow-up.

At the time of the initial neck recurrence, 3 patients were treated with repeat surgery and 2 were on active surveillance, and none received additional RAI therapy. Of the 3 patients who were treated, 2 achieved no evidence of disease and 1 patient had a second neck recurrence by the end of the follow-up. The 2 patients on active surveillance after the initial neck recurrence continued to have stable persistent disease by the end of the follow-up. Thus, at the end of the follow-up period (median: 3 years), 1 had recurrent disease, 2 had persistent but stable structural disease, and 2 had no evidence of disease after repeat surgery.

Table 4. Characteristics of the 5 patients who had a recurrence by end of follow-up

Age, years	Sex	Histology of the primary tumor	Size of the primary tumor, cm	Vascular invasion	Extrathyroidal extension	Other foci, n	Size of the other foci, cm	Affected N1b nodes	Affected N1a nodes	Largest affected node	Extranodal extension
26	M	Classic	2.2	Focal	Present	>20	<0.1–1.4	40	10	2.7	Yes
28	F	Classic	2.5	None	Absent	2	<0.1–1.1	11	0	2.5	Yes
36	M	Classic	2.5	None	Present	4	<0.1–1.8	41	11	1.8	Yes
57	F	Tall cell	4.5	None	Absent	2	0.4–2.5	2	6	2.0	Yes
79	F	Tall cell	1.8	None	Present	2	0.4–1.2	0	0	N/A	N/A

M = Male; F = female; N/A = not available.

Table 5. Other characteristics of the 5 patients who had a recurrence by the end of follow-up

Iodine-131 activity for ablation, mCi	AJCC stage	Modified 2009 ATA initial risk	Best response to the initial therapy	Status at the final follow-up	Follow-up time, months	Time to recurrence, years	Site of recurrence
150	I	High	Biochemical incomplete	Recurrent disease	15	9 and 15	Neck
290	I	High	Biochemical incomplete	No evidence of disease	23	11	Neck
373	I	Intermediate	Indeterminate	Structural persistent disease	29	26	Neck
152	III	Intermediate	Excellent	No evidence of disease	6	5	Neck
157	III	Intermediate	Biochemical incomplete	Structural persistent disease	2.5	2	Neck

Discussion

To our knowledge, this is the first study to describe the natural history of multifocal macroscopic papillary thyroid cancer without gross extrathyroidal extension. We found that the risk of recurrence in this cohort was low (6%), similar to that in patients with multifocal microscopic PTC or that of classic papillary thyroid cancer (1–4 cm) without extrathyroidal extension or nodal involvement. All of the recurrences were in the neck and none of our patients developed distant metastasis or died from thyroid cancer, supporting a low-risk behavior of this presentation.

As predicted, the vast majority of patients with multifocal macroscopic PTC (91%) had no evidence of disease or an indeterminate response at the final follow-up. Almost all of the the patients with N0 disease had no clear structural evidence of thyroid cancer recurrence or persistent disease after the initial therapy or on follow-up, and none developed distant metastasis (fig. 1). When we examined patients with N1 disease, those at risk for distant metastasis were detected at diagnosis and none developed distant metastasis on follow-up. Also, 4 of the 5

patients who recurred had bulky nodal involvement in the lateral neck with extranodal extension at diagnosis. Therefore, as clinicians, we can easily identify early on in the disease process the small proportion of patients with multifocal macroscopic papillary thyroid cancer at risk for distant metastasis or a future recurrence.

As shown in tables 4 and 5, we observed that recurrence tends to occur late (the median time to recurrence was 11 years, with all but 1 patient having a recurrence after 9 years of follow-up), suggesting the need for long-term follow-up especially in patients presenting with bulky nodal involvement at diagnosis. One patient with multifocal macroscopic PTC without nodal involvement had a structural recurrence 2 years after his initial therapy after achieving a biochemical incomplete response. It can be argued that this patient had persistent disease after the initial therapy that went undetected and did not truly recur.

Our data are in concordance with most series reporting long-term follow-up of thyroid microcarcinoma patients [17, 18]. In the paper by Baudin et al. [7] about thyroid microcarcinoma, multivariate analysis showed that the only 2 parameters that influenced recurrence were the

number of thyroid microcarcinoma foci at pathologic examination and the extent of the initial thyroid surgery. Hay et al. [17] identified initial lymph node metastases and the extent of the initial thyroid surgery as the 2 risk factors for locoregional recurrence in a multivariate analysis of 535 patients with thyroid microcarcinoma [17]. In a prior series of 148 patients, examining the prognostic factors of papillary microcarcinoma, our group demonstrated that tumor multifocality, among other factors, correlated with the presence of metastatic nodes at diagnosis. In turn, the presence of significant nodal involvement (>3 affected nodes) strongly correlated with a worse recurrence-free survival ($p < 0.001$). One patient with poorly differentiated nodal metastasis died in that series [19]. In the current study of multifocal macroscopic PTC, we observed that almost all recurrences were also due to (or strongly interrelated with) bulky nodal involvement at diagnosis but did not correlate with the number of thyroid cancer foci.

Based on the review of the literature, the 2015 ATA risk classifier for structural disease specific recurrence (fig. 4 of the 2015 ATA guidelines) estimates that the risk of recurrences of unifocal intrathyroidal papillary thyroid microcarcinoma (1–2%), multifocal papillary thyroid microcarcinoma (4–6%), and intrathyroidal papillary thyroid cancer sized between 2 and 4 cm and irrespectively of multifocality (~5%) is low [10]. Our study suggests that patients with macroscopic multifocal PTC

without gross extrathyroidal extension or clinically significant lymph node metastases can be similarly classified as ‘low risk’.

We recognize that our study is limited by its retrospective design and the short median follow-up. Thus, we may have detected more recurrences if our cohort had been followed for more than 10 years. We propose that patients with multifocal macroscopic papillary thyroid cancer who present with bulky nodal involvement be treated with complete resection and RAI adjuvant therapy and remain under close follow-up for a long period of time (exceeding 15 years) as recurrences tend to occur late.

In conclusion, patients presenting with multifocal macroscopic papillary thyroid cancer without bulky nodal involvement or gross extrathyroidal extension have a low risk of thyroid cancer-specific recurrence and mortality.

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Disclosure Statement

No competing financial interests exist for Dr. Sabra. Dr. Tuttle is a consultant for Genzyme.

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