Multifocality in Sporadic Medullary Thyroid Carcinoma: An International Multicenter Study

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Background: Current surgical standard of care in sporadic medullary thyroid carcinoma (sMTC) consists of a minimum of total thyroidectomy with central neck dissection. Some have suggested thyroid lobectomy with isthmusectomy and central neck dissection for patients with sMTC, given their lower frequency of bilateral disease, although this topic has not been thoroughly studied. This study assessed the prevalence of multifocality in sMTC via a large international multi-institutional retrospective review to quantify this prevalence, including the impact of geography, to assess more accurately the risks associated with alternative surgical approaches.

Methods: A retrospective chart review of sMTC patients from 11 institutions over 29 years (1983–2011) was undertaken. Data regarding focality, extent of disease, *RET* germline analysis plus family and clinical history for multiple endocrine neoplasia type 2 (MEN2), and demographic data were collected and analyzed.

Results: Patients from four continents and seven countries were included in the sample. Data for 313 patients with documented sMTC were collected. Of these, 81.2% were confirmed with negative *RET* germline testing, while the remaining 18.8% demonstrated a negative family history and no manifestations of MEN2 syndromes other than MTC. Bilateral disease was identified in 17/306 (5.6%) patients, while multifocal disease was noted in 50/312 (16.0%) sMTC patients. When only accounting for germline negative patients, these rates were not significantly different (5.6% and 17%, respectively). Among them, when disease was unifocal in the ipsilateral lobe and isthmus, bilateral disease was present in 6/212 (2.8%) cases. When disease was multifocal in the ipsilateral lobe or isthmus, then bilateral disease was present in 8/37 (21.6%) cases ($p < 0.001$). No geographic differences in focality were identified.

Conclusions: The 5.6% prevalence of bilateral foci in sMTC suggests that total thyroidectomy should remain the standard of care for initial surgery, as less complete thyroid surgery may fail to address fully the primary site of disease. Whether ipsilateral tumor focality should be an independent factor determining the need for completion thyroidectomy when sMTC is diagnosed after hemithyroidectomy remains to be determined.

Keywords: multifocality, medullary thyroid carcinoma, humans, thyroid neoplasm, surgery

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Introduction

MEDULLARY THYROID CARCINOMA (MTC) accounted for 2.2% of all thyroid cancer in a database of 43,644 thyroid cancer cases from 1992 to 2006 in the United States (1), and historically is observed sporadically in approximately 75–80% of patients while the remainder have a hereditary form (multiple endocrine neoplasia type 2 [MEN2], including the familial MTC variant) (2) transmitted with autosomal dominant patterns of inheritance by mutation of the *REarranged during Transfection (RET)* proto-oncogene (3–7).

Surgery is the only curative treatment for both hereditary and sporadic forms of MTC, and its chance of success is greatest when the disease is confined to the thyroid, or when minimal lymph node metastatic disease is present (8). Total thyroidectomy, central neck dissection, and therapeutic dissection of involved lateral neck compartments, with or without prophylactic dissection of clinically uninvolved compartments (levels II–V), is the current recommended treatment for patients with MTC (2,9). Because the hereditary form of MTC is due to an oncogenic germline mutation in the *RET* proto-oncogene, virtually all patients are at risk for bilateral and multifocal disease (10–12), which justifies the need for total thyroidectomy, whether prophylactic (ideal) or therapeutic. Therapeutic total thyroidectomy in addition to lymph node dissection has also been generally recommended for patients with sporadic MTC (sMTC). However, it has been noted that tumor multifocality and bilaterality occurs less frequently compared with the hereditary form (12). Based upon these findings, the argument has been made for unilateral thyroidectomy (lobectomy and isthmusectomy) with a lymph node dissection for sMTC that is confined to one lobe (13), shortening operating time and potentially lowering the risks of hypoparathyroidism, hypothyroidism, recurrent laryngeal nerve injury, voice changes, and other surgical complications compared with total thyroidectomy (14–21).

The prevalence of bilateral foci in sMTC has been reported to range widely from 0% to 66.7% (13,22–37), though these reports were not all based upon germline DNA testing to exclude MEN2. Several studies from single institutions have more systematically applied *RET* mutation testing and standardized pathological analyses to investigate the occurrence of multifocal or bilateral disease more accurately among sMTC patients. Still, most of these patient cohorts were small, and some inconsistent results were seen (Table 1). The objective of this investigation was to evaluate the prevalence, and possible correlation, of multifocality and bilaterality in sMTC. A large, international, multi-institutional retrospective investigation was conducted to quantify this occurrence in a large and diverse population to limit random or biased findings from small cohorts and to test the impact of geography. These analyses allow the role of alternative surgical approaches in the current treatment of sMTC to be considered.

Methods

Institutional Review Board approval and center recruitment

Institutional Review Board (IRB) approval was obtained from the primary author's institution prior to proceeding. Next, a data collection sheet was generated with explicit instructions for de-identified data collection to standardize data

input. Fifty-three institutions in 11 countries were invited to participate in data collection. IRB approval was obtained from each participating institution per their institutional protocols. Subsequently, the data were reviewed for internal agreement and standardized for data analysis. The seventh edition of the American Joint Committee on Cancer's (AJCC) staging manual was utilized for tumor staging (38).

Data collection, definitions, and inclusion criteria

Retrospective chart review was performed on all patients with a diagnosis of MTC at each institution, and data were collected for all patients with sMTC. sMTC was defined as MTC in either (i) the presence of a negative *RET* germline analysis, or (ii) the absence of a family history of MTC and no evidence of other manifestations of MEN syndromes. Demographic data are reviewed in Table 2. Bilateral disease in sMTC was defined as the presence of the sMTC diagnosis in foci in both lobes of the thyroid gland. Cases of multifocal disease within one lobe and the isthmus were not included in this definition. Only cases in which a pathologist assessed both thyroid lobes were included in the assessment of bilateral disease, excluding patients who did not undergo surgery after diagnosis of sMTC due to medical comorbidities and patients who underwent unilateral thyroid lobectomy without completion thyroidectomy. Multifocal disease in sMTC was defined as the presence of the sMTC diagnosis in more than one pathologic focus within the thyroid gland, either in the same lobe or the contralateral lobe. By definition, all bilateral cases were considered multifocal. Only patients who did not undergo surgery after diagnosis of sMTC were excluded.

Statistical analysis

Bilateral and multifocal sMTC cases were identified. The number and percentage of each (denominator = all included sMTC cases based on above described criteria) are reported with exact binomial confidence intervals for the percentage calculated for each. Counts and percentages with exact binomial confidence intervals are also reported by study site, FNA result, T stage, N stage, M stage, and age quartile. Within each of these categories, chi-square tests were performed to assess differences in bilateral and multifocal disease. Significant omnibus chi-square tests were followed up with all pairwise comparisons by chi-square or Fisher's exact tests, as appropriate. All tests were evaluated at the $\alpha = 0.05$ significance level. Data were analyzed using SAS/STAT[®] v9.2 (SAS Institute, Inc., Cary, NC).

Results

Subject recruitment

Of the 53 institutions invited, 13 agreed to participate, and 11 ultimately submitted data. Responding institutions represented seven nations and four continents. From these centers presenting for management from 1983 to 2011, 313 patients with biopsy-proven sMTC were identified. One patient elected for nonoperative management of biopsy-proven sMTC and was excluded from this analysis. The remaining 312 operated patients were included in analyses of multifocality. Average age at first surgical intervention was 52 ± 15 years (range 19–101 years). While 81.2% of patients had negative *RET* proto-oncogene testing supporting sMTC, the

TABLE 1. SUMMARY OF LITERATURE EVALUATING MULTIFOCAL AND/OR BILATERAL sMTC

Lead author	Year	Total patients	Total sMTC	% Bilateral disease	% Multifocal disease	Definition of sMTC	Publication country of origin
Zedenius (27)	1995	46	46	n/a	4.3	Clinically sporadic, no familial occurrence; two with multifocality and C-cell hyperplasia; germline tested exons 10, 11, 16, and negative	Sweden
Scopsi (22)	1996	109	93	21.5	43	Negative familial screening for MTC or pheochromocytoma, and basal or pentagastrin-stimulated calcitonin	Italy
Beressi (23)	1998	899	83	3.9 ^a	20	Isolated MTC, no familial history of MTC or MEN2, no bilateral C-cell hyperplasia	France
Kebebew (24)	2000	104	58	66.7	n/a	No relative with MEN2; 17% without germline mutation in exons 10, 11, 13, and 14	United States
Dolan (28)	2000	38	23 ^b	0	0	Not explicitly stated	Ireland
Weber (29)	2001	36	16	n/a	19	Not explicitly stated	Germany
Kaserer (30)	2001	50	34	8.8	8.8	Not carriers of mutations in exons 10, 11, and 13–16	Austria
Miyauchi (13)	2002	94	40	0	18.3 ^c	No familial occurrence, MEN2 or germline <i>RET</i> mutation	Japan
Miyauchi (13)	2002	94	20	5	18.3 ^c	Apparently sporadic, no familial occurrence or MEN2, but no <i>RET</i> testing	Japan
Scollo (31)	2003	101	54	13	n/a	Absent germline mutation when screened, negative familial MTC and pentagastrin screening	France
Guyétant (32)	2003	66	27	3.7	14.8	Not carriers of mutations in exons 8, 10, 11, 13–16	France
Hamy (33)	2005	43	43	n/a	25.6	Not carriers of mutations in exons 10, 11, 13–16	France
Chow (34)	2005	22	19	10.5	21.1	All 12 patients with multifocal or bilateral disease germline tested (three mutated)	Hong Kong
Gulben (25)	2006	32	32	28	n/a	Physical examination, absence of pheochromocytoma, no familial occurrence, normal serum calcium	Turkey
Machens (37)	2007	232	126	4.8	8	Not carriers of mutations in exons 10, 11, and 13–16	Germany
Scheuba (35)	2007	97	88	21.6	22.7	Not carriers of mutations in exons 5, 8, 10, 11, and 13–16	Austria
Moura (36)	2009	52	51	n/a	25	Not carriers of mutations in exons 5, 8, and 10–16	Portugal
Current Study	2016	312	312	5.6	16	No familial occurrence, MEN2 or germline <i>RET</i> mutation (81.2% tested)	International

^aOnly micro sMTC included in analysis, bilaterality in 3/76 who underwent bilateral surgery.

^bTwenty-three patients were noted to have sMTC; only nine underwent total thyroidectomy, allowing evaluation of both focality and laterality.

^cReported only among the combined cohorts (n = 60) as intraglandular metastases.

sMTC, sporadic medullary thyroid carcinoma; MEN2, multiple endocrine neoplasia type 2.

remaining 18.8% were untested and classified as sMTC based upon negative family history and absence of other findings of MEN syndromes. Six patients underwent thyroid lobectomy alone and were excluded from analysis of bilateral disease (n = 306; Fig. 1).

Bilateral disease

Of the 306 sMTC patients who underwent bilateral thyroid surgery, 17 (5.6%) [confidence interval (CI) 3.3–8.8%] dem-

onstrated pathologic evidence of bilateral disease. Of these, documentation of the dimensions of the secondary tumor were only included for 10/17 specimens. For the subset of bilateral tumors, the median size of the primary site was 1.6 cm (range 0.3–7.2 cm), while the largest contralateral MTC focus was 0.8 cm (range 0.06–4.8 cm). When only accounting for germline *RET* negative patients, bilateral disease was present in 14/249 patients (5.6% [CI 3.1–9.3%]). In patients without germline *RET* mutations, when disease was unifocal in the ipsilateral lobe and isthmus, bilateral disease

TABLE 2. DEMOGRAPHIC, PATHOLOGIC, AND TREATMENT INFORMATION COLLECTED FOR EACH SUBJECT

Median age at initial surgery	51 years (range 19–101 years)
<i>RET</i> oncogene testing status	
Negative	253 (81.1)
Not tested	59 (18.9)
Preoperative clinical diagnosis	
MTC	106 (34)
Possible MTC	6 (1.9)
Other ^a	200 (64.1)
Extent of thyroidectomy	
Total thyroidectomy	256 (82.1)
Lobectomy with completion	50 (16)
Lobectomy only	6 (1.9)
Extent of central neck dissection	
Prophylactic	Ipsilateral 93 (29.8); contralateral 73 (23.4)
Therapeutic	Ipsilateral 87 (27.9); contralateral 76 (24.4)
Not done	Ipsilateral 93 (29.8); contralateral 124 (39.7)
Unable to assess	Ipsilateral 39 (12.5); contralateral 39 (12.5)
Extent of lateral neck dissection	
Prophylactic	Ipsilateral 40 (12.8); contralateral 15 (4.8)
Therapeutic	Ipsilateral 90 (28.8); contralateral 32 (10.3)
Not done	Ipsilateral 162 (51.9); contralateral 252 (80.8)
Unable to assess	Ipsilateral 20 (6.4); contralateral 13 (4.2)
TNM stage based upon AJCC 7th edition	All tumors: $n=312$; multifocal: $n=50$; bilateral: $n=17$
Stage I	All tumors: 93 (29.8); multifocal: 7 (14); bilateral: 3 (17.6)
Stage II	All tumors: 58 (18.6); multifocal: 0 (0); bilateral: 0 (0)
Stage III	All tumors: 22 (7.1); multifocal: 5 (10); bilateral: 1 (5.9)
Stage IVa	All tumors: 87 (27.9); multifocal: 21 (42); bilateral: 8 (47.1)
Stage IVb	All tumors: 4 (1.3); multifocal: 2 (4); bilateral: 1 (5.9)
Stage IVc	All tumors: 44 (14.1); multifocal: 14 (28); bilateral: 3 (17.6)
Unable to stage	All tumors: 4 (1.3); multifocal: 1 (2); bilateral: 1 (5.9)
Extrathyroidal extension (at any focus)	
Present	83 (26.6)
Not present	215 (68.9)
Unknown	14 (4.4)
Lymphovascular invasion	
Present	109 (34.9)
Not present	158 (50.6)
Unknown	45 (14.4)
Tumor maximum dimension	
Primary tumors	20 mm (range 1–120 mm) in 286 (91.7%); not recorded in 26 (8.3%)
Contralateral tumors	8 mm (range 0.6–48 mm) in 9 (52.9%); not recorded in 8 (47.1%)
Number and location of tumor foci ^b	
Ipsilateral	$N=286/312^c$; median = 1; range 0–11 ^d
Isthmus	$N=9/17^c$; median = 0; range 0–2
Contralateral	$N=10/17^c$; median = 0; range 0–3
Dimensions of sMTC foci ^b	
Ipsilateral	$N=301/286^c$; median = 18; range 0–120 ^d
Isthmus	$N=10/9^c$; median = 6; range 2–40
Contralateral	$N=11/9^c$; median = 6; range 0.6–48

Values are presented as n (%) or median (range) as appropriate.

^aDetails are provided on the subset of 245 patients who underwent preoperative fine-needle aspiration in Essig *et al.* (39).

^bCalculated from patients with specific information regarding size and number of foci available.

^cNumber of patients with specific data reported/number of patients with disease reported in the location (e.g., 17 patients had disease reported in the contralateral lobe, but only 10 reported the exact number and size of foci present).

^dSeveral patients with primary tumor in isthmus with no reported lobe focus were assigned “0” for the number and size of ipsilateral foci.

^eNumber of foci with specific data reported/number of patients with discrete data reported. (e.g., the exact number and size of foci in the contralateral lobe were reported in 9 patients, which totaled to 11 foci). The numerator exceeds the denominator due to multifocality in the location.

TNM, tumor, node, metastasis staging system; AJCC, American Joint Committee on Cancer.

FIG 1. Schematic accounting for all patients identified in this retrospective multi-center study.

was present in 6/212 (2.8%) cases. When disease was multifocal in the ipsilateral lobe or isthmus, then bilateral disease was present in 8/37 (21.6%) cases ($p < 0.001$).

Staging analysis. When prevalence of bilateral sMTC was analyzed in terms of the seventh edition of AJCC TNM staging, there was no linear association with increasing T stage and prevalence of bilateral disease. However, a statistically significant increase in the prevalence of bilateral sMTC was noted when comparing T4a, T4b, and T3 sMTC with T2 disease ($p = 0.02$ for each comparison; Table 3). There was no significant difference between T2 and lower stage disease in the prevalence of bilateral disease. There was no association between nodal status or metastatic status and prevalence of bilateral sMTC.

TABLE 3. BILATERAL sMTC ANALYSIS BY T STAGE

<i>T stage</i>	<i>Bilateral/all sMTC</i>	<i>CI</i>
0–1a ^a	5/77 (6.5%)	2–15%
1b	1/51 (2.0%)	0–10%
2	0/71 (0%)	0–5%
3	5/61 (8.2%)*	3–18%
4a ^a	3/26 (11.5%)*	2–30%
4b	2/11 (18.2%)*	2–52%
X	1/9 (11.1%)	0–48%

Staging based upon AJCC 7th edition. Comparisons not statistically significant unless stated.

^aT0–1a includes one patient with a nodal focus of sMTC without disease identified in the thyroid, and one patient quantified as T1 but not further characterized. T4a includes four patients quantified as T4 but not further characterized.

* $p = 0.02$.

CI, confidence interval; X, stage unknown.

Age analysis. Age quartiles were not significantly associated with prevalence of bilateral sMTC. However, the majority of bilateral sMTC (11/17; 64.7%) was noted in the younger half of the sample.

Regional analysis. The prevalence of bilateral sMTC among the sites surveyed ranged broadly (0–17.7%; Table 4), but there was no statistically significant difference in prevalence among the sites ($p = 0.72$).

Multifocal disease

For analysis of multifocal disease, the original 313 patients were reviewed, and only the single patient who elected nonoperative management was excluded. Of the remaining 312 patients, 50 were found to have multifocal disease (16% [CI 12–21%]; Fig. 1). Of these 50 multifocal patients, 17 had bilateral disease, 42 were multifocal only on the ipsilateral side, and one was multifocal ipsilaterally but did not undergo resection of the contralateral lobe to allow bilaterality to be determined. When only accounting for known germline *RET* negative patients, multifocal disease (not bilateral) was present in 11.5% (29/253) of patients, and unifocal tumors were found in 83% (210/253) of patients.

Staging analysis. When prevalence of multifocal sMTC was analyzed in terms of the seventh edition of the AJCC TNM staging (38), there was no linear association with increasing T stage and prevalence of bilateral disease. However, a statistically significant increase in the prevalence of multifocal sMTC was noted when comparing T4a, T4b, and T3 sMTC with T2 disease ($p = 0.001$, 0.002, and 0.004, respectively). Multifocality was also significantly more common in T4b disease compared with T3, T1b, and T0–1a disease ($p = 0.03$, 0.04, and 0.001, respectively). Remaining comparisons between T stages were not significantly different (Table 5). Multifocal

TABLE 4. BILATERAL sMTC ANALYSIS BY REGION

Country	Site	Bilateral/ all sMTC	CI
Australia	Melbourne	3/17 (17.7%)	4–43%
Brazil	Sao Paulo ^a	3/70 (4.3%)	1–12%
Greece	Athens	0/7 (0%)	0–41%
Holland	Multiple sites	0/21 (0%)	0–16%
Italy	Catanzaro	0/10 (0%)	0–31%
	Naples	0/11 (0%)	0–28%
	Rome	4/34 (11.8%)	3–27%
	Sienna	3/56 (5.4%)	1–15%
United Kingdom	Birmingham	1/21 (4.8%)	0–24%
United States	Columbus, OH	2/48 (4.2%)	1–14%
	Madison, WI	1/11 (9.1%)	0–41%

There was no statistically significant difference in prevalence among the sites ($p=0.72$).

^aExons 8, 10, 11, and 13–16 of the *RET* gene were sequenced in their entirety. Forty-five of these patients underwent testing exons 1–7, 9, 12, 17, 18, and 19, and part of a 50 sMTC patient study that found no additional causative mutations (40).

disease was also significantly more common in N1b compared with N0 patients ($p<0.001$). There were no other significant associations with nodal status (Table 6). With respect to metastatic disease, there was a significantly greater prevalence of multifocality in those with distant metastatic disease compared with those without ($p=0.001$; Table 6).

Age analysis. The prevalence of multifocal sMTC in the youngest quartile of the sample (26%) was significantly greater than the third and fourth quartiles (8% and 9%, respectively; $p=0.003$ and $p=0.01$ for each comparison).

Regional analysis. The prevalence of multifocal sMTC among the sites surveyed ranged broadly (0–24%), but there was no statistically significant difference in prevalence among the sites ($p=0.23$; Table 7).

Discussion

Total thyroidectomy with central neck dissection, with or without lateral neck dissection, is a well-established treat-

TABLE 6. MULTIFOCAL sMTC ANALYSIS BY NODAL AND METASTATIC STAGING

	Multifocal/all sMTC	CI
<i>N stage</i>		
0	4/85 (5%)	0–8%
1a ^a	5/32 (16%)	0–16%
1b	37/121 (31%)*	5–17%
X	4/74 (5%)	0–9%
<i>M stage</i>		
0	15/121 (12%)	7–20%
1	16/44 (36%)*	22–52%
X	19/147 (13%)	8–20%

Staging based upon AJCC 7th edition. Comparisons not statistically significant unless stated.

^aN1a includes five patients quantified as N1 but not further characterized.

* $p<0.001$; ** $p=0.001$.

ment for patients with MTC (2). This is well supported in patients with hereditary MTC who present with clinical disease or significantly elevated serum calcitonin levels, as there is a high prevalence of tumor bilaterality and multifocality, necessitating removal of the thyroid gland in its entirety (2). Total thyroidectomy is also recommended in sMTC, despite the fact that the disease tends to be a unicentric process confined to one lobe. This is historically justified by the possibilities of bilateral primary disease or intraglandular metastases, the possibility of inherited disease when *RET* proto-oncogene testing has not been performed or was negative, and to optimize surgical access for bilateral central neck lymph node dissection (10–12). Still, some authors have recommended hemithyroidectomy (lobectomy with isthmusectomy) with central and ipsilateral lateral neck dissection based on the absence of *RET* proto-oncogene mutation and on the macroscopic extent of the primary tumor (13,41). Ito *et al.* managed a series of patients with this approach in Japan, and reported clinical outcomes better than those from Western countries, and none of their patients showed disease

TABLE 5. MULTIFOCAL sMTC ANALYSIS BY T STAGE

T stage	Multifocal/all sMTC	CI
0–1a ^a	11/79 (14%)	7–24%
1b	6/52 (12%)	4–23%
2	4/72 (6%)	1–14%
3	14/62 (23%)*	13–35%
4a ^a	8/26 (31%)*	14–52%
4b	6/11 (55%)*	23–83%
X	1/10 (10%)	0–45%

Staging based upon AJCC 7th edition. Comparisons not statistically significant unless stated.

^aT0–1a includes one patient with a nodal focus of sMTC without disease identified in the thyroid, and one patient quantified as T1 but not further characterized. T4a includes four patients quantified as T4 but not further characterized.

* $p=0.004$; ** $p=0.002$; *** $p=0.03$, <0.001 , 0.04 , and 0.001 compared with T3, T2, T1b, and T1a, respectively.

TABLE 7. MULTIFOCAL sMTC ANALYSIS BY REGION

Country	Site	Multifocal/ all sMTC	CI
Australia	Melbourne	4/17 (24%)	7–50%
Brazil	Sao Paulo ^a	10/71 (14%)	7–24%
Greece	Athens	1/7 (14%)	0–58%
Holland	Multiple sites	1/21 (5%)	0–24%
Italy	Catanzaro	0/10 (0%)	0–31%
	Naples	0/12 (0%)	0–26%
	Rome	8/35 (23%)	10–40%
	Sienna	11/56 (20%)	10–32%
United Kingdom	Birmingham	1/21 (5%)	0–24%
United States	Columbus, OH	11/49 (22%)	12–37%
	Madison, WI	3/13 (23%)	5–54%

No statistically significant difference in prevalence among the sites ($p=0.23$).

^aExons 8, 10, 11, and 13–16 of the *RET* gene were sequenced in their entirety. Forty-five of these patients underwent testing exons 1–7, 9, 12, 17, 18, and 19 and part of a 50 sMTC patient study that found no additional causative mutations (40).

recurrence in the thyroid remnant (41). These authors noted that previous treatment recommendations focused more on the debate of using central and lateral nodal dissection, while their approach instead focused on the extent of thyroidectomy (while all patients underwent ipsilateral central and lateral neck dissections). Total thyroidectomy (as well as bilateral central neck dissection) places the bilateral recurrent and superior laryngeal nerves and all parathyroid glands at risk. In comparison, hemithyroidectomy (lobectomy with isthmusectomy) and ipsilateral central neck dissection places only the ipsilateral nerves at risk and lowers the risk of permanent hypoparathyroidism by leaving undisturbed parathyroid tissue on the contralateral side. Further, hemithyroidectomy significantly reduces the risk of long-term hypothyroidism requiring thyroid hormone replacement compared with bilateral thyroidectomy (21). In the surgical treatment for sMTC, these surgical risks must be weighed against the risk of persistent disease. Regarding the currently recommended extent of thyroid surgery according to guidelines, the American Thyroid Association (ATA) and the National Comprehensive Cancer Network (NCCN) recommend total thyroidectomy as opposed to hemithyroidectomy (2,9). In patients diagnosed with apparent sMTC following a hemithyroidectomy, these guidelines indicate that *RET* germline mutation status, serum calcitonin, and the results of imaging studies should determine the role of completion thyroidectomy (2,9). It is important to note that this approach does not include tumor focality in this consideration. This may be particularly relevant for patients with multifocal disease in the ipsilateral lobe or isthmus, as 21.6% of them were found to be harboring disease in the contralateral lobe. While serum calcitonin and ultrasonography may safely indicate the need for completion thyroidectomy (immediately or subsequently) in similar patients treated with a hemithyroidectomy, especially those with macroscopic MTC in the remaining lobe, it is unknown if patient outcomes are impaired by not including tumor multifocality as an independent clinical factor to guide the completion thyroidectomy decision. In the present cohort, the median size of the largest contralateral MTC focus was 8 mm (range 0.6–48 mm), suggesting that a significant fraction of patients with bilateral disease would have had negative or inconclusive preoperative ultrasound findings of the contralateral lobe. It is also important to recognize that bilateral disease did occur, even in sMTC patients with unifocal disease in the ipsilateral lobe and isthmus, suggesting that all patients who chose to be treated with an initial lobectomy require at least ongoing careful surveillance.

The consequences of persistent disease are believed to be significant. Complete surgical resection when the disease is confined to the neck is currently the only curative treatment of MTC (sporadic or hereditary) (11,42). Residual primary tumor in a remaining thyroid lobe could potentially give rise to metastatic foci, a disease state associated with a significantly reduced rate of biochemical cure. Duh *et al.* reported that patients who underwent less surgery than routine total thyroidectomy and central neck dissection have been shown to require more reoperations (43). In a study evaluating prognostic factors in sMTC, Gulben *et al.* reported in a multivariate analysis that the extent of the primary surgical resection was an independent risk for survival (25). Patients with incomplete resection had a 4.8 times higher risk of death

than those who had a complete resection. In their sample, 28% of tumors were noted to be bilateral. Panigrahi *et al.* reported that patients receiving surgery discordant with ATA guideline recommendations had shorter survival than those receiving surgery according to recommendations (44). Still, not all studies support these findings. Esfandiari *et al.* reported that for tumors ≤ 2 cm without distant metastases, overall survival was not altered by surgical intervention, while all surgical interventions similarly improved survival compared to no surgery for tumors >2 cm without distant metastases (45).

The frequency of bilateral disease in sMTC varies widely from 0% to 66.7%, as illustrated in Table 1, although the frequency was lower in series with more thorough germline *RET* proto-oncogene testing (13,22–36). The present findings show that 17/306 (5.6%) patients had bilateral disease, which is comparable to the median value of 7.2% among the previous reports shown in Table 1. To account for any geographical variances in focality and bilaterality, 313 patients with biopsy proven sMTC were identified from 11 centers within seven nations and four continents. The prevalence of bilateral sMTC among the sites surveyed ranged broadly (0–18%; Table 4). There were no statistically significant differences in prevalence among the geographic locations. Although there was no linear association with increasing T stage and prevalence of bilateral disease, there was a statistically significant increase in the prevalence of bilateral sMTC when comparing advanced T stage lesions with T2 tumors. Still, among T2 and lower tumors, the prevalence of bilaterality was 4.5%.

Multifocal tumors have also been shown to be independent risk factors for nodal metastasis, and may explain why tumor size alone does not always predict lymph node metastasis (23,37). Multifocal disease was found to be significantly more common in N1b compared with N0 patients ($p < 0.001$). With respect to distant metastatic disease, there was a significantly greater prevalence of multifocality in those with metastatic disease compared with those without. The prevalence of multifocal sMTC in the youngest quartile of the sample (26%) was significantly greater than the third and fourth quartiles. One may speculate that this is due to unrecognized hereditary MTC, despite their negative family histories, or negative germline *RET* proto-oncogene analysis. Lindsey *et al.* studied 50 patients for this question (40), 45 of whom are included in this study. Their 50 patient cohort had been screened by sequencing exons 8, 10, 11, and 13–16 of the *RET* gene in their entirety. Still, 27 patients had one or more features suggesting familial disease, such as a young age of onset of MTC (<35 years of age; 16 patients), tumor multifocality (13 patients), or the presence of C cell hyperplasia (10 patients). Four patients had both young age at diagnosis (in these cases <30 years old) and multifocal disease. Those 50 patients underwent extended *RET* testing of exons 1–7, 9, 12, and 17–19 with the identification of no new causative mutations. The present study identified multifocal tumors in 50/312 (16%) patients, which is consistent with the median value of 18.3% among the prior studies shown in Table 1 (range 0–43%). There were no statistically significant differences in prevalence among the geographic locations. As with bilateral disease, there was no linear association with increasing T stage and prevalence of multifocal disease. As with bilateral disease, there was a statistically significant

increase in the prevalence of multifocal sMTC when comparing advanced versus early T-staged tumors.

The strengths of the current study of the rate of multifocality and bilaterality for clinically sMTC include the large number of patients accrued from 11 centers across seven countries, most of whom had negative *RET* germline testing. To the authors' knowledge, this is the largest study of its kind. The geographic diversity of the patients provides balance to institutional discrepancies and establishes a broad benchmark for the prevalence of multifocal and bilateral disease in sMTC. Preoperative analysis of *RET* gene mutation is an important point of differentiation, as up to 17% of patients with apparent sMTC with no family history or diagnostic criteria for MEN2A have been found to harbor germline *RET* gene mutations (26). While separate results for the entire cohort and those with known negative analyses for germline *RET* mutations are provided, these results were not statistically different. Only 3/17 patients with bilateral disease did not undergo germline *RET* mutational analysis.

The limitations of the current study include its retrospective nature and the lack of standardized protocol in assessing surgical specimens (such as number of tissue sections examined or use of calcitonin immunohistochemistry) or extent of *RET* gene analysis (e.g., rare or newly identified variants associated with inherited MTC may not have been investigated). Most familial MTC cases are identified when testing the most commonly affected exons, so additional testing for rare mutations is unlikely to change the findings meaningfully. In Tables 4 and 7, it should be noted that the Sao Paulo site contributed the largest fraction of patients to this study and routinely sequenced exons 8, 10, 11, and 13–16 of the *RET* gene in their entirety, and 45 of these patients also underwent extended testing of exons 1–7, 9, 12, 17, 18, and 19 (40). The Sao Paulo rates of bilaterality and multifocality are consistent with those of the entire cohort, and add credibility and generalizability to the findings. Additional limitations include the lack of standardized use and extent of lymph node surgery in sMTC among the participating centers, and the N stage may have been underestimated in patients who did not undergo maximal lymph node dissection. Finally, 312 patients were included in the analyses of multifocality, and 306 patients in the analyses of bilaterality. The difference was that six patients underwent only hemithyroidectomy (Fig. 1). Unifocal disease was found in five of these patients, and multifocal disease in the remaining patient. These five (or six) patients could have been excluded from the multifocality analyses, since the status of the contralateral lobe was unknown, although it is unlikely that the findings would have changed significantly, as the unifocal patients would have required finding disease in the contralateral lobe to change their focality status, and the data demonstrate that the prevalence of this occurring is low.

Conclusion

On average, 1/18 patients with sMTC have bilateral tumor foci in the thyroid gland. This finding supports the ATA and NCCN guideline recommendations that total thyroidectomy should remain the initial standard of care as opposed to hemithyroidectomy. In patients diagnosed with apparent sMTC following a hemithyroidectomy, these guidelines indicate that *RET* germline mutation status, serum calcito-

nin, and the results of imaging studies should determine the role of completion thyroidectomy (2, 9). sMTC patients with multifocal MTC in the ipsilateral thyroid lobe or isthmus have a significant prevalence of MTC in the contralateral lobe. It remains unknown if ipsilateral tumor focality should be included as an independent factor when considering completion thyroidectomy.

Author Disclosure Statement

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