Benefit-Risk Balance of Reoperation for Persistent Medullary Thyroid Cancer

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Objective: This investigation aimed at exploring the prospects of a cure for persistent medullary thyroid cancer (MTC) stratified by basal calcitonin levels before reoperation and the number of lymph node metastases previously removed at outside facilities.

Background: There is no evidence-based information supporting the balance of surgical benefit and risk in persistent MTC.

Methods: This retrospective study of 334 patients with persistent MTC referred to a tertiary surgical center, who were compared with 367 patients with previously untreated MTC referred to that institution during the same time period, evaluated biochemical cure rates after systematic lymph node dissection.

Results: The relationship between the incremental serum calcitonin level before reoperation and the number of lymph node metastases at reoperation and biochemical cure was strong after previous removal of 0 ($r = 0.74$ and 77%–0%) and 1 to 5 lymph node metastases ($r = 0.61$ and 60%–0%) elsewhere. It disappeared once more than 5 lymph node metastases had been cleared at other hospitals (nonsignificant and 5%). When serum calcitonin levels were 1000 pg/mL or lower before reoperation, biochemical cure rates were 44% (59 of 133 patients) and 18% (12 of 65 patients) after previous removal of 0 and 1 to 5 lymph node metastases, respectively. These rates plummeted to 5% (2 of 43 patients) after a previous clearance of more than 5 lymph node metastases. When serum calcitonin levels exceeded 1000 pg/mL before reoperation, a biochemical cure was exceptional (1%; 1 of 76 patients).

Conclusions: With serum calcitonin levels of 1000 pg/mL or lower before reoperation and the previous removal of 5 or fewer lymph node metastases, systematic lymph node dissection seems worthwhile for persistent MTC. These findings will need to be validated in independent series before being adopted more widely as a new standard of care.

Keywords: biochemical risk stratification, cervical reoperation, basal calcitonin, compartment-oriented surgery, distant metastasis, lymph node metastasis, medullary thyroid carcinoma, postoperative hypoparathyroidism, recurrent laryngeal nerve palsy

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Medullary thyroid cancer (MTC) cells, deriving from the neural crest, are able to synthesize, store, and release calcitonin into the bloodstream. As a natural consequence, basal (ie, unstimulated) serum calcitonin levels, which are easily measurable by taking a venous blood sample, parallel the overall tumor load. The determination of this tumor load usually requires a combination of extensive neck surgery and imaging. Because of its propensity to spread to lymph nodes early on, MTC can present the surgeon with a formidable challenge regarding the adequate extent of the initial operation. On preoperative neck ultrasonography, more than one-third of patients with MTC (8 of 22 patients; 36%) were found to have false-negative findings.[1] These false-negatives affected more frequently the central (7 of 22 patients; 32%) than the lateral (3 of 22 patients; 14%) neck. When reoperation is contemplated for persistent MTC, these rates are believed to be much worse due to extensive scarring from the initial neck surgery.

In previously untreated patients, preoperative serum calcitonin levels representing a biologic continuum, correlated fairly well with the primary tumor size, the number of lymph node metastases, and postoperative normalization of increased calcitonin levels, commonly referred to as "biochemical cure."[2–4] In the largest series of patients with previously untreated MTC to date, lymph node metastases were present in the ipsilateral central and lateral neck, contralateral central neck, contralateral lateral neck, and upper mediastinum, respectively, beyond basal calcitonin thresholds of 20, 50, 200, and 500 pg/mL. Bilateral compartment-oriented neck surgery reached biochemical cure in at least half the patients with pretherapeutic basal calcitonin levels of 1000 pg/mL or lower but not in patients with levels greater than 10000 pg/mL.[3]

These rates of biochemical cure and involvement of the central and lateral neck and upper mediastinum, originating from patients with previously untreated MTC, are unlikely to extend to those select patients with persistent MTC whose increased serum calcitonin levels failed to normalize after initial neck surgery. Without pertinent data, the prospects of a cure for patients with persistent (and hence, often more advanced) disease are widely perceived as being poor, often not warranting reoperation in the absence of symptomatic or clearly progressive or threatening cervical metastases.[5] Because 10 or more involved nodes are almost always incompatible with biochemical cure,[6–8] the total number of all lymph node metastases removed elsewhere may modify the predictive value of the increased serum calcitonin levels before reoperation.

This investigation, setting the scene for patients with persistent MTC in need of reoperation, was devised to explore the prospects of cure for persistent MTC stratified by (i) basal calcitonin levels before reoperation at this institution and (ii) the number of lymph node metastases previously removed at outside hospitals.

PATIENTS AND METHODS

Study Population

A total of 784 consecutive patients (403 patients for previously untreated tumors and 381 patients for persistent tumors) underwent (re-)operations for MTC between November 1994 and December 2011 at the Department of General, Visceral and Vascular Surgery in Halle (Saale), Germany. No systematic lymph node dissection had been carried out in 19 patients with previously untreated MTC (15 gene carriers and 4 patients with incidental medullary thyroid microcarcinoma measuring no more than 6 mm at the greatest dimension) and 15 patients with persistent MTC who, having had extensive systematic lymph node dissections elsewhere, required only a focused surgical approach to clear a target lesion. An additional 17 and 32 patients had no preoperative serum calcitonin levels measured in-house, leaving 367 patients (91%) and 334 patients (88%) for analysis.

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The latter 334 patients with persistent MTC, entailing a higher risk meriting a thorough examination, were contrasted with the aggregate data of all 367 patients with previously untreated MTC, a reference group believed to carry a lower risk. The detailed clinical-pathological characteristics of 300 of these 367 patients with previously untreated MTC have been described elsewhere.[3] Among all of the 701 patients with systematic lymph node dissection included in this study, there were 389 women and 312 men with sporadic (487 patients) or hereditary (214 patients) disease. These patients were evaluated together because patients with sporadic and hereditary MTC have comparable serum calcitonin levels after adjustment for the extent of disease.[9]

Measurements of Serum Biomarkers

Serum calcitonin levels were routinely measured at this institution until May 2004 with the ELSA-hCT solid 2-site immunoradiometric calcitonin assay (CIS Bio International, Gif-sur-Yvette, France; normal range <10 pg/mL). After May 2004, the Immulite 2000 automated calcitonin assay (Diagnostic Products Corporation, Los Angeles, CA), enabling determination of calcitonin levels immediately before surgery, replaced the ELSA-hCT assay (normal range of the Immulite 2000 assay is <5 pg/mL for women and <8.4 pg/mL for men). The Immulite 2000 and ELSA-hCT calcitonin assays are both linearly related to the Nichols-Advantage assay,[10,11] rendering the respective calcitonin measurements comparable.

Postoperatively, calcitonin stimulation was carried out as needed to evaluate the adequacy of the initial neck surgery and the absence of residual disease. Calcitonin levels were stimulated using a slow intravenous bolus injection of 0.5 μg pentagastrin per kilogram of body weight (Peptavlon, Laboratoires SERB, Paris, France) or, more recently, 2.5 mg calcium gluconate per kilogram of body weight over 2 minutes, taking as the peak calcitonin level the higher of the 2 or the 5-minute calcitonin level after stimulation. Normalization of serum calcitonin was assumed when the upper normal limit of the respective calcitonin assay (10 pg/ml for either sex and <5 pg/mL for women or <8.4 pg/mL for men, respectively) was not exceeded basally.

Compartment-Oriented Surgery

All operations were conducted using optical magnification and bipolar coagulation, as described previously.[12,13] Informed consent was obtained before each operation that represented standard practice of care in accordance with the practice guidelines of the German Society of Surgery.[14] Distant metastases per se were not an exclusion criterion because of the recognized longevity of patients with metastatic medullary thyroid cancers.

Histopathological Examination and Tumor Staging

After gross evaluation by the pathologist, the entire thyroid gland was divided vertically to separate the left and right lobes. The thyroid halves were then sectioned horizontally from the superior to the inferior pole, as described elsewhere.[15] After fixation in formalin, the whole thyroid gland was embedded in paraffin. Soft tissue and lymph nodes were processed separately. Conventional staining (hematoxylin and eosin) and calcitonin immunohistochemistry were performed on every surgical specimen, using the standard avidin-biotin complex peroxidase approach and a commercial polyclonal antibody (Immunotech, Marseilles, France). A diagnosis of MTC was made from evidence of tumor extension beyond the basement membrane, a demonstration of lymphatic or vascular invasion on histopathology, or a combination thereof. Pathology reports from outside institutions were reviewed as necessary. A diagnosis of MTC was made from evidence of tumor extension beyond the basement membrane, a demonstration of lymphatic or vascular invasion on histopathology, or a combination thereof according to the World Health Organization's International Histological Classification of Tumours.[16,17] Primary tumor diameter was ascertained by direct measurements on the surgical thyroid specimens. When multiple medullary thyroid cancers were present, only the largest tumor was considered. Aggregate counts of involved and removed nodes were calculated by summing up the numbers of histopathologically confirmed nodes documented for each operation at this institution or elsewhere. Distant metastasis was diagnosed when there was unequivocal evidence on ultrasonography, computed tomography, magnetic resonance imaging, positron emission tomography, or any combination thereof, regardless of when it was noted.

Data Analysis

Categorical and continuous data were tested with the 2-tailed χ^2 test and 1-way analysis of variance, respectively. The level of significance (all tests were 2-sided) was set at less than 0.05. Spearman rank correlation coefficient was calculated to evaluate the correlation between various brackets of serum calcitonin levels (<10; 10–100; 101–500; 501–1000; 1001–5000; >5000 pg/mL), considering the number of patients available for analysis, and the number of lymph node metastases as a continuous variable. A similar strategy was pursued to categorize the number of previously removed lymph node metastases in increments of 0, 1 to 5, and more than 5 nodes, striking a balance between the number of observations available and a sufficient level of detail. The pattern of lymph node metastases was evaluated by dividing histopathologically node-positive lymph node compartments by the total number of lymph node compartments, counting undissected compartments as node-negative for the purpose of this study. This conservative approach yielded minimum estimates of compartmental involvement.

RESULTS

Clinical and Histopathological Characteristics of Previously Untreated MTC and Persistent MTC

As depicted in Table 1, the 334 patients referred with persistent MTC differed in many ways from the 367 patients referred with previously untreated MTC: largest primary tumor diameter (means of 23.2 vs 15.5 mm; $P < 0.001$), numbers of previously involved (means of 0.5 vs 0.1 involved nodes; $P < 0.001$) and previously dissected nodes (means of 0.6 vs 0.1 nodes; $P < 0.001$), which had been removed elsewhere for diagnostic or therapeutic reasons; positive nodal status (83% vs 42%; $P < 0.001$); distant metastasis (20% vs 12%; $P = 0.004$); and basal calcitonin levels before (re-)operation at this institution (means of 1797 vs 3979 pg/mL; $P = 0.014$). Although disparate numbers of nodes were cleared from patients with previously untreated MTC and persistent MTC (means of 43.2 vs 53.8 nodes; $P < 0.001$), 21% and 13% ($P = 0.002$) of which included mediastinal lymph node dissection as well, these (re-)operations yielded similar numbers of lymph node metastases (means of 6.8 vs 6.8 involved nodes; $P = 0.96$). Overall, summing up all the nodes cleared at any time, patients with persistent MTC had more nodes involved (means of 11.3 vs 7.2 nodes; $P < 0.001$), resulting in much reduced rates of biochemical cure (23% vs 64%; $P < 0.001$).

Involved and Dissected Nodes and Biochemical Cure in Patients Referred With Previously Untreated MTC and Persistent MTC

Table 2 illustrates the significant ($P < 0.001$) relationships between incremental calcitonin levels before the initial operation and reoperation, respectively, and (i) more lymph node metastases ($r = 0.64$ and $r = 0.63$; Spearman rank coefficient) and (ii) declining rates of biochemical cure (100%–2% and 75%–0%, respectively). These relationships were comparable in nature among patients referred with

TABLE 1. Clinical and Histopathological Characteristics of 701 Patients With Previously Untreated MTC or Persistent MTC

Category	Variable Examined	Initial Operation (367 Patients)	Reoperation (334 Patients)	*P*
Demographics	Age at tissue diagnosis, mean [95% CI], y	45.9 [43.6–47.9]	45.6 [44.0–47.1]	0.82
	Sex, male, n (%)	167 (46)	145 (43)	0.60
Biomarker	Basal calcitonin level before (re-)operation at this institution, mean [95% CI] pg/mL	3979 [2545–5413]	1797 [858–2736]	0.014
Thyroid pathology	Largest primary tumor diameter, mean [95% CI], mm*	15.5 [13.9–17.0]	23.2 [21.6–24.8]	<0.001§
	Extrathyroidal extension, n (%)	75 (20)	71 (21)	0.64
Previous lymph node dissection elsewhere	Involved nodes before (re-)operation at this institution, mean [95% CI], n†	0.1 [0–0.1]	0.5 [0.4–0.5]	<0.001§
	Removed nodes before (re-)operation at this institution, mean [95% CI], n†	0.1 [0–0.1]	0.6 [0.5–0.6]	<0.001§
Systematic lymph node dissection at this institution	Positive nodal status, n (%)	155 (42)	278 (83)	<0.001§
	Central neck dissection, n (%)	352 (96)	308 (92)	0.033
	Lateral neck dissection (ipsilateral), n (%)	286 (78)	283 (85)	0.026
	Lateral neck dissection (contralateral), n (%)	272 (74)	246 (74)	0.86
	Mediastinal lymph node dissection, n (%)	46 (13)	71 (21)	0.002§
	Involved nodes at this institution, mean [95% CI], n	6.8 [5.3–8.4]	6.8 [5.6–8.0]	0.96
	Removed nodes at this institution, mean [95% CI], n	53.8 [50.1–57.4]	43.2 [40.1–46.3]	<0.001§
Outcome	Involved nodes after all operations, mean [95% CI], n†	7.2 [5.6–8.9]	11.3 [9.7–12.9]	<0.001§
	Removed nodes after all operations, mean [95% CI], n†	54.8 [51.1–58.5]	58.0 [54.8–61.2]	0.20
	Distant metastasis, n (%)	45 (12)	68 (20)	0.004
	Biochemical cure, n (%)‡	215 (64)	74 (23)	<0.001§

CI indicates confidence interval.
*Excluding 16 and 37 patients with no information on primary tumor diameter, respectively.
†Excluding 1 and 12 patients with no or only incomplete information on previous lymph nodes, respectively.
‡Excluding 28 and 17 patients with no information on biochemical cure, respectively.
§Statistically significant after correction for multiple testing.

TABLE 2. Involved and Dissected Nodes and Biochemical Cure Stratified by Serum Calcitonin Level Before (Re-)Operation at this Institution

Preoperative Calcitonin Level, pg/mL	Involved Nodes, Mean [95% CI], n			Removed Nodes, Mean [95% CI], n			Biochemical Cure, n (%)*‡		
	Initial Operation (367 Patients)	Reoperation (334 Patients)	*P*	Initial Operation (367 Patients)	Reoperation (334 Patients)	*P*	Initial Operation (339 Patients)	Reoperation (317 Patients)	*P*
<10	0.7 [0–2.3]	0.5 [0.2–0.8]	0.63	22.4 [8.2–36.7]	35.0 [27.5–42.4]	0.09	21 (100) [100]	40 (75) [77]	0.015
10–100	0.3 [0–0.5]	3.0 [1.5–4.5]	<0.001	34.7 [28.2–41.1]	51.9 [45.4–58.4]	<0.001	87 (92) [92]	19 (27) [30]	<0.001
101–500	1.6 [0.9–2.4]	6.1 [4.4–7.7]	<0.001	59.8 [53.0–66.7]	41.8 [35.8–47.8]	<0.001	60 (83) [85]	9 (11) [14]	<0.001
501–1000	7.4 [4.1–10.7]	9.0 [5.9–12.1]	0.48	67.1 [56.6–77.6]	43.6 [35.4–51.8]	0.001	20 (53) [59]	5 (13) [17]	<0.001
1001–5000	8.2 [5.3–11.0]	11.3 [8.2–14.3]	0.14	62.1 [56.1–68.0]	41.2 [33.2–49.2]	<0.001	27 (40) [47]	1 (2) [3]	<0.001
>5000	29.1 [21.0–37.2]	21.1 [12.1–30.1]	0.21	74.4 [63.3–85.4]	44.9[30.9–59.0]	0.002	1 (2) [5]	0 (0) [0]	>0.99
P	<0.001	<0.001		<0.001	0.035 (0.18†)		<0.001	<0.001	
r	0.64	0.63		0.43					

CI indicates confidence interval; r, Spearman correlation coefficient.
*Excluding 28 and 17 patients with no information on biochemical cure, respectively.
†Statistically nonsignificant after exclusion of all patients with preoperative calcitonin levels of <10 pg/mL.
‡Percentages in parentheses are based on all patients, whereas percentages in brackets exclude all patients with evidence of distant metastases.

previously untreated MTC and patients referred with persistent MTC. Patients with persistent MTC and increased calcitonin levels of 5000 pg/mL or lower harbored more lymph node metastases and had significantly worse rates of biochemical cure than patients with previously untreated MTC. Beyond that threshold, these differences were reversed (means of 21.1 vs 29.1 dissected nodes) or leveled (biochemical cure in 0% vs 2%). The exclusion of patients with evidence of distant metastasis improved only marginally the percentage of biochemically cured patients in either group (Table 2).

Among patients with persistent MTC and increased calcitonin levels of 10 pg/mL or higher, there was no significant correlation between the number of dissected lymph nodes and the various brackets of calcitonin levels (means of 41.2–51.9 dissected nodes; $P = 0.18$). In contrast, patients with previously untreated MTC showed

a significant correlation between preoperative calcitonin levels and the number of lymph nodes removed (means of 22.4–74.4 dissected nodes; $P < 0.001$; Table 2). This correlation ($r = 43$) was weaker than the correlation between the preoperative calcitonin levels and the number of lymph node metastases removed ($r = 0.64$). This finding implied that the extent of lymph node dissection did not confound the relationship between the preoperative calcitonin levels and lymph node metastases in these patients, obviously because our comprehensive lymph node dissection cleared most, if not all, residual lymph node metastases in the neck.

Nodes Involved on Reoperation and Biochemical Cure Stratified by Serum Calcitonin Level Before Reoperation and Previously Involved Nodes

As anticipated, the number of residual lymph node metastases and the corresponding decline in biochemical cure rates depended not only on the calcitonin levels before reoperation but also on the number of previously removed lymph node metastases (Table 3). The relationship between the incremental serum calcitonin level before reoperation and the number of lymph node metastases found at reoperation and biochemical cure was close after previous removal of 0 ($r = 0.74$ and 77%–0%; Table 3, left panel) and 1 to 5 lymph node metastases ($r = 0.61$ and 60%–0%; Table 3, intermediate panel) but disappeared once more than 5 lymph node metastases had been cleared at the initial operation (nonsignificant and 5%; Table 3, right panel).

When serum calcitonin levels were 1000 pg/mL or lower before reoperation, biochemical cure rates were 44% (59 of 133 patients) and 18% (12 of 65 patients) after previous removal of 0 and 1 to 5 lymph node metastases, respectively. These rates plummeted to 5% (2 of 43 patients) after previous clearance of more than 5 lymph node metastases. When serum calcitonin levels exceeded 1000 pg/mL before reoperation, biochemical cure was exceptional (1%; 1 of 76 patients). The exclusion of patients with evidence of distant metastasis did little to improve these rates: 50% (59 of 118 patients), 21% (12 of 57 patients), and 6% (2 of 34 patients) after previous removal of 0, 1–5, and >5 lymph node metastases among patients with preoperative calcitonin levels of 1000 pg/mL or lower, and 2% (1 of 44 patients) in the presence of calcitonin levels higher than 1000 pg/mL.

Irrespective of whether 0, 1 to 5, or more than 5 lymph node metastases had been previously removed, the number of dissected lymph nodes at reoperation was not significantly different across the various brackets of increased calcitonin levels (means of 42.0–56.2 removed nodes, $P = 0.28$; means of 36.8–62.0 removed nodes, $P = 0.16$; and means of 21.2–44.2 removed nodes, $P = 0.45$, respectively), ruling out a correlation between the number of dissected lymph nodes and the various brackets of increased calcitonin levels.

Involved Lymph Node Compartments Stratified by Serum Calcitonin Level Before Reoperation and Previously Involved Nodes

Table 4 presents a breakdown of the minimum involvement of the central and lateral neck and the upper anterior mediastinum by the incremental calcitonin levels before reoperation, stratified by the previous removal of 0, 1 to 5, and more than 5 lymph node metastases elsewhere. After previous removal of 0 and 1 to 5 (but not >5) lymph node metastases, rates of involvement in the central and lateral neck progressed significantly across the various brackets of serum calcitonin levels before reoperation. From a clinical perspective, however, this relationship was not discriminatory enough to make informed decisions regarding the necessary extent of systematic dissection in the neck and mediastinum (Table 4).

Surgical Complications Stratified by Previously Involved Nodes

When surgical complications sustained elsewhere before referral to this institution were stratified by the number of previously removed lymph node metastases (0; 1–5; >5 involved nodes), the rates of preexisting hypoparathyroidism surged significantly from 1.7% to 6.0% to 12.8% ($P = 0.001$; Table 5). Like trends were noted for complete unilateral (14.5%, 21.7%, and 23.1%; $P = 0.07$), incomplete unilateral (3.5%, 0%, and 6.4%; $P = 0.029$), and bilateral recurrent laryngeal nerve palsy (0.6%, 0%, 2.6%; $P = 0.10$), all of which were too weak to survive correction for multiple testing. The 3 patients with preexistent bilateral recurrent laryngeal nerve palsy required laryngoplastic procedures before reoperation. These high rates of preexistent recurrent nerve palsy (18.5%, 21.7%, and 32.1%; $P = 0.014$) explain why patients referred with persistent MTC tended to have the central neck dissected less often than those patients

TABLE 3. Nodes Involved on Reoperation and Biochemical Cure Stratified by Serum Calcitonin Level Before Reoperation and Number of Previously Removed Lymph Node Metastases

	Number of Lymph Node Metastases Removed Before Reoperation (334 Patients)								
	0			1–5			5		
Preoperative Calcitonin Level, pg/mL	Patients, n	Nodes Involved on Reoperation, Mean [95% CI]	Biochemical Cure, n (%)*,‡	Patients, n	Nodes Involved on Reoperation, Mean [95% CI]	Biochemical Cure, n (%)*,‡	Patients, n	Nodes Involved on Reoperation, Mean [95% CI]	Biochemical Cure, n (%)*,‡
<10	50	0.5 [0.2–0.8]	36 (77) [77]	6	0.5 [0–1.1]	3 (60) [75]	1	2 [–]	1 (–) [–]
10–100	42	1.8 [1.1–2.4]	13 (33) [36]	19	2.8 [1.2–4.5]	6 (33) [35]	12	7.8 [0–16.7]	0 (0) [0]
101–500	37	7.4 [4.4–10.4]	7 (21) [26]	30	5.5 [3.0–8.0]	1 (3) [4]	18	4.3 [1.8–6.8]	1 (6) [9]
501–1000	12	12.0 [3.6–20.4]	3 (25) [38]	13	6.2 [3.2–9.2]	2 (15) [20]	15	8.9 [3.8–14.0]	0 (0) [0]
1001–5000	22	11.6 [7.6–15.7]	0 (0) [0]	8	14.0 [6.7–21.3]	0 (0) [0]	23	10.0 [4.1–15.9]	1 (4) [6]
5000	10	20.7 [14.9–26.5]	0 (0) [0]	7	37.3 [3.6–70.9]	0 (0) [0]	9	8.9 [1.3–16.5]	0 (0) [0]
P	173	<0.001	<0.001	83	<0.001	<0.001	78	0.57†	0.38†
r		0.74			0.61			-	

CI indicates confidence interval; r, Spearman correlation coefficient.

*Excluding 10, 4, and 3 patients with no information on biochemical cure, respectively.

†Excluding the only patient with a preoperative calcitonin level of <10 pg/mL.

‡Percentages in parentheses are based on all patients, whereas percentages in brackets exclude all patients with evidence of distant metastases.

TABLE 4. Involved Lymph Node Compartments Stratified by Serum Calcitonin Level before Reoperation and Number of Previously Removed Lymph Node Metastases

Previously Involved Nodes	Preoperative Calcitonin Level, pg/mL	Patients, n	Involvement of Lymph Node Compartment, n (%)*			
			Central Neck	Lateral Neck (Ipsilateral)	Lateral Neck (Contralateral)	Upper Anterior Mediastinum
0	<10	50	6 (12)	8 (16)	1 (2)	0 (0)
	10–100	42	19 (45)	18 (43)	3 (7)	0 (0)
	101–500	37	25 (68)	23 (62)	7 (19)	5 (14)
	501–1000	12	7 (58)	9 (75)	3 (25)	1 (8)
	1001–5000	22	16 (73)	15 (68)	7 (32)	8 (36)
	>5000	10	8 (80)	8 (80)	6 (60)	2 (20)
	P		<0.001‡	<0.001‡	<0.001‡	<0.001‡
1–5	<10	6	3 (50)	0 (0)	0 (0)	0 (0)
	10–100	19	10 (53)	10(53)	1 (5)	1 (5)
	101–500	30	18 (60)	20 (67)	3 (10)	3 (10)
	501–1000	13	8 (62)	8 (62)	4 (31)	1 (8)
	1001–5000	8	8 (100)	6 (75)	2 (25)	1 (13)
	>5000	7	2 (29)	6 (86)	5 (71)	1 (14)
	P		0.004‡	<0.001‡	<0.001‡	0.09
>5	<10	1	—	—	—	—
	10–100	12	5 (42)	5 (42)	2 (17)	1 (8)
	101–500	18	10 (59)	10 (56)	6 (33)	1 (6)
	501–1000	15	6 (40)	12 (80)	5 (33)	3 (20)
	1001–5000	23	12 (52)	16 (70)	7 (30)	7 (30)
	>5000	9	6 (67)	5 (56)	3 (33)	4 (44)
	P†		0.16	0.023	0.27	0.002‡

*Counting undissected lymph node compartments as free of lymph node metastases.
†Excluding the only patient with a preoperative calcitonin level of <10 pg/mL.
‡Statistically significant after correction for multiple testing.

TABLE 5. Surgical Complications after Reoperation Stratified by Number of Previously Removed Lymph Node Metastases

Postoperative Surgical Complications				Number of Lymph Node Metastases Removed Before Reoperation (334 Patients)			
				0 (173 Patients)	1–5 (83 Patients)	5 (78 Patients)	*P*
Before reoperation (preexistent)	Recurrent laryngeal nerve palsy, n (%)	Unilateral	Complete	25 (14.5)	18 (21.7)	18 (23.1)	0.07
			Incomplete	6 (3.5)	0	5 (6.4)	0.029
		Bilateral	Any	1 (0.6)	0	2 (2.6)	0.10
		Total	Any	32 (18.5)	18 (21.7)	25 (32.1)	0.014
	Hypoparathyroidism, n (%)		Preexistent	3 (1.7)	5 (6.0)	10 (12.8)	0.001‡
After reoperation	Recurrent laryngeal nerve palsy, n (%)	Unilateral	Complete	1 (0.6)	2 (2.4)	5 (6.4)	0.006‡
			Incomplete	8 (4.6)	0 (0)	3 (3.8)	0.033
		Bilateral	Any	0	0	0	—
		Total	Any	9 (5.2)	2 (2.4)	8 (10.3)	0.027
	Hypoparathyroidism, n (%)*		Postoperative†	21 (12.4)	8 (10.3)	8 (11.8)	0.55
	Unilateral palsy of other cervical nerves, n (%)		Sympathetic plexus	2 (1.2)	1 (1.2)	2 (2.6)	0.46
			Accessory nerve	0 (0)	0 (0)	2 (2.6)	0.05
	Complications requiring reoperation, n (%)		Hemorrhage/hematoma	8 (4.6)	6 (7.2)	2 (2.6)	0.16
			Wound infection/abscess	4 (2.3)	3 (3.6)	2 (2.6)	0.77
			Seroma/lymphatic leakage	5 (2.9)	3 (3.6)	0 (0)	0.12

*Based on 170, 78, and 68 patients with no pre-existent hypoparathyroidism and no calcium and/or vitamin D substitution before reoperation.
†Requiring calcium and/or vitamin D substitution after reoperation.
‡Statistically significant after correction for multiple testing within each type of complication.

referred with previously untreated MTC (92% vs 96%; $P = 0.033$; Table 1), in the face of the generally more comprehensive extent of these reoperations. Across successive increments of previously removed lymph node metastases, our rates of new-onset complete postoperative vocal cord palsy also moved up significantly, though on a much lower scale: from 0.6% to 2.4% to 6.4% ($P = 0.006$; Table 5). Yet these rates represented no more than one fifth of those complications patients were referred with for completion. There was no instance of postoperative bilateral recurrent laryngeal nerve palsy after reoperation at this institution. Unilateral complete vocal cord palsy was the sole surgical complication after reoperation to remain significant after correction for multiple testing.

DISCUSSION

Systematic lymph node dissection in the neck can offer important benefits, first and foremost the prospect of biochemical cure. The one-time cost of reaching a definitive cure and the cost of daily thyroxine supplementation may be smaller from a societal perspective than the need for continual biochemical follow-up and imaging studies, some of which may prompt additional operations at incremental costs. If biochemical cure is beyond reach, as in the presence of distant metastases, the focus of surgical treatment shifts to the maintenance of locoregional control in the neck.

Before planning a surgical procedure, the potential benefits to be gained from the operation (biochemical cure and locoregional control) need to be balanced against the attendant surgical risks (permanent recurrent laryngeal nerve palsy and hypoparathyroidism). This principle becomes even more important when one ponders systematic lymph node dissection for persistent cancer in a scarred operative field. For uncommon conditions, including persistent MTC, evidence-based data supporting this difficult trade-off are rarely, if ever, available. Nevertheless, the benefit of a reoperation for residual MTC usually outweighs the generally limited risk of surgical morbidity in experienced hands.[18–20] This investigation provides, for the first time, detailed information about the balance of the surgical benefit and risk in persistent MTC.

Balance of Surgical Benefit and Risk in Persistent MTC

As long as patients with persistent MTC reveal serum calcitonin levels of 1000 pg/mL or lower before reoperation and have 5 or fewer lymph node metastases cleared at the initial operation, systematic lymph node dissection seems worthwhile and reasonably safe in experienced hands. Systematic lymph node dissection performed for the completion of an inadequate previous operation can afford biochemical cure rates in the range of 18% to 44% with acceptable surgical morbidity. Once 1 of 2 threshold criteria (>1000 pg/mL before reoperation or >5 previous lymph node metastases) has been exceeded, biochemical cure rates are as low as 1% to 5%, with surgical morbidity on the rise. In this setting, the question becomes whether to embark on a systematic lymph node dissection in an effort to improve locoregional control at the expense of greater surgical morbidity, or whether to pursue a focused approach directed at target lesions lodging in strategically critical positions at a reduced surgical risk. This dispute cannot be settled in the absence of long-term outcome studies enrolling large numbers of patients in either treatment arm. Such studies would also need to be adjusted for many confounding clinical-pathological variables while ensuring a sufficient number of events of locoregional recurrence. Under these circumstances, this point should be frankly discussed, deferring to the personal preferences of the patients who will need to make a value judgment on whether to trade, or not to trade a somewhat higher surgical risk for a possible long-term improvement of locoregional control in the neck.

Limitations of the Study

This investigation has many limitations, all of which attest to the complexity of the clinical situation. Patients with persistent MTC are extremely hard to standardize, many of whom present with major surgical complications from previous operations, most often recurrent laryngeal nerve palsy. There is clearly a fine line between tumor invasion of the recurrent laryngeal nerve and soft tissue infiltrations in the nerve's close proximity, tempting some surgeons to dissect the tumor off the nerve to preserve its function where other surgeons would sacrifice a functional nerve to eradicate the tumor. This kind of decision eludes surgical standardization. Because usually the side of the primary tumor is affected, surgical completion of the other side can be challenging. In these patients, interests of safety (preservation of the contralateral recurrent laryngeal nerve's function), trumping standardization, frequently enforce modifications of an otherwise systematic approach to the neck. In such an environment, a prospective randomized trial does not seem feasible given the inherent requirement for adhering to a stringent clinical protocol. Moreover, the inadequacy of the previous neck operation carried out elsewhere is difficult, if not impossible, to standardize for a rare condition.

To complicate the matter further, the quality of the outside pathology reports in this study was varied, some of them lacking detailed information on the location (frequently) and the number of involved and dissected lymph nodes (infrequently). These details can become relevant in the event of reoperation, informing the extent of dissection in the neck (systematic lymph node dissection versus a focused surgical approach). This observation suggests that there is still some room for improvement in the collaboration between surgeons and pathologists.

On a cautionary note, our findings, having been obtained at a tertiary referral center, may not be generalizable to community hospitals or regional hospitals that do not have the necessary technical equipment (bipolar forceps coagulation, nerve monitoring devices, magnification glasses) or the surgical and technical skills necessary for the mastery of a high-risk procedure for an evasive disease.

Future Perspectives

The unfeasibility of a prospective randomized trial renders our retrospective findings even more important. Of note, the extent of systematic dissection, based on the number of lymph nodes removed in this study, did not differ according to serum calcitonin levels of 10 pg/mL or higher before reoperation (means of 41.2–51.9 nodes; Table 2), supporting the internal validity of our results. Although this investigation included as many as 334 patients with persistent MTC, our findings will need to be validated in independent series before being adopted more widely as a new standard of care.

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