Biomarker-Based Risk Stratification for Previously Untreated Medullary Thyroid Cancer

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Context: Preoperative neck ultrasonography may yield false-negative findings in more than one-third of medullary thyroid cancer (MTC) patients. If not cleared promptly, cervical lymph node metastases may emerge subsequently. Reoperations entail an excess risk of surgical morbidity and may be avoidable.

Objective: This comprehensive investigation aimed to evaluate in a head-to-head comparison the clinical utility of pretherapeutic biomarker serum levels (basal calcitonin; stimulated calcitonin; carcinoembryonic antigen) for indicating extent of disease and providing biochemical stratification of pretherapeutic MTC risk.

Design: This was a retrospective analysis.

Setting: The setting was a tertiary referral center.

Patients: Included were 300 consecutive patients with previously untreated MTC.

Interventions: The intervention was compartment-oriented surgery.

Main Outcome Measure: Stratified biomarker levels were correlated with histopathologic extent of disease.

Results: Higher biomarker levels reflected larger primary tumors and more lymph node metastases. Stratified basal calcitonin serum levels correlated better ($r = 0.59$) with the number of lymph node metastases than carcinoembryonic antigen ($r = 0.47$) or pentagastrin-stimulated calcitonin ($r = 0.40$) levels. 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 achieved biochemical cure in at least half the patients with pretherapeutic basal calcitonin levels of 1,000 pg/ml or less but not in patients with levels greater than 10,000 pg/ml.

Conclusions: Most newly diagnosed MTC patients, *i.e.* those with pretherapeutic basal calcitonin levels greater than 200 pg/ml, may need bilateral compartment-oriented neck surgery to reduce the number of reoperations. (***J Clin Endocrinol Metab* 95: 2655–2663, 2010**)

Because of its propensity for lymph node and distant metastases, medullary thyroid cancer (MTC) has been notoriously difficult to cure if not diagnosed early on. Traditionally, high-resolution neck ultrasonography has been advocated to preoperatively confirm or exclude cervical lymph node metastases in MTC patients (1). Remarkably, more than one third of previously untreated MTC patients (eight of 22 patients; 36%) reveal false-negative findings during preoperative neck ultrasonography (1). These false-negative findings occur more often in the central (7 of 22 patients; 32%) than the lateral (three of 22 patients; 14%) neck compartment. If not dissected

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Abbreviations: CEA, Carcinoembryonic antigen; MTC, medullary thyroid cancer.

promptly, these lymph node metastases may surface subsequently, necessitating reoperations in a scarred neck at an excess risk of surgical morbidity. After initial neck surgery, the rates of false-negative ultrasonographic findings are even higher: 44% (27 of 61 patients) before reoperation for recurrent MTC, and 49% (19 of 39 patients) before reoperation for persistent MTC (1). The imperfection of preoperative neck ultrasonography, which tends to overlook lymph node metastases in more than one third of MTC patients, is calling for alternative operative strategies.

As a tribute to their neuroendocrine heritage, malignant C cells retain the capacity to synthesize and store calcitonin in dense vesicules (2), from which it is released after iv injection of pentagastrin or calcium. MTC cells produce carcinoembryonic antigen (CEA) as well (2). As a membrane-bound protein, CEA is released into the bloodstream by the tumor cells at a fairly constant rate. Basal calcitonin and CEA serum levels, which are easily ascertained preoperatively by simply taking a venous blood sample, correlate with overall tumor burden, such as primary tumor diameter, lymph node, and distant metastases (3–6), and cancer-specific survival, which is bleaker for patients revealing serum calcitonin and CEA doubling times of less than 6 months (7–9). For early tumor detection, routine measurements of basal calcitonin levels have been recommended in patients with thyroid nodules, with the addition of pentagastrin stimulation for those exceeding certain thresholds (10–15).

Before being adopted more widely for stratification of preoperative risk and determination of the required extent of surgery, more precise information is needed regarding the utility of these serum biomarkers in the preoperative setting. The objectives of this comprehensive study of a large cohort of previously untreated MTC patients were 2-fold: 1) to assess, in a head-to-head comparison, the suitability of basal calcitonin levels *vs.* stimulated calcitonin levels *vs.* CEA levels as indicators of primary tumor size and lymph node metastases, and 2) to clarify the clinical utility of pretherapeutic serum levels of the best suitable diagnostic biomarker for indicating the involvement of cervical and mediastinal lymph node compartments, providing a biochemical stratification of pretherapeutic risk.

Patients and Methods

Study population

A total of 630 consecutive patients (317 patients for previously untreated tumors and 313 patients for recurrent or persistent tumors) underwent operations for MTC between September 1995 and September 2009 at the Department of General, Visceral, and Vascular Surgery in Halle (Saale), Germany. For the purpose of this investigation, all 300 of the 317 MTC patients with initial operations (95%) who underwent systematic lymph node dissection of at least the central lymph node compartment were considered.

There were 169 women and 131 men with sporadic (175 patients) and hereditary (125 patients) disease. These patients were evaluated as one group because patients with sporadic and hereditary MTC have similar biomarker levels after correction for extent of disease (5). Of these 300 study patients, 97 (32%), 95 (32%), 89 (30%), and 77 (26%) patients, respectively, had been included in previous publications on basal calcitonin (5, 16), stimulated calcitonin (17), or CEA serum levels (6).

Measurements of serum biomarkers

Serum calcitonin levels were routinely measured at this institution between September 1995 and May 2004 with the ELSA-hCT solid two-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 Corp., 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 (Nichols Institute Diagnostics, San Juan Capistrano, CA) (18, 19), rendering the respective calcitonin measurements comparable with each other.

Stimulation of calcitonin levels was carried out by injecting 0.5 μg pentagastrin per kilogram body weight (Peptavlon; Laboratoires SERB, Paris, France) as an iv bolus, taking as peak calcitonin level the higher of the 2- or 5-min calcitonin level after stimulation. Preoperatively, pentagastrin stimulation was performed in some but not all MTC patients with increased basal calcitonin levels to confirm the diagnosis (17) so that stimulated calcitonin levels were not available for all patients. Postoperatively, pentagastrin stimulation was carried out to evaluate the adequacy of initial neck surgery and the absence of residual disease.

CEA levels were determined with the same monoclonal electroluminescence immunoassay (Elecsys; Roche Diagnostics, Mannheim, Germany; upper normal limit <4.6 ng/ml). Because the Elecsys assay was introduced at this institution in July 1997, fewer MTC patients had CEA than basal calcitonin levels.

Total thyroidectomy and compartment-oriented surgery

All 300 study patients (100%) had total thyroidectomy with systematic lymph node dissection of the central neck compartment using the compartment-oriented approach (20). The lateral neck compartments had been dissected systematically in 227 patients (76%) ipsilateral to, and in 217 patients (72%) also contralateral to the largest primary thyroid tumor. Systematic lymph node dissections of the mediastinal compartment had been carried out in 44 of the 300 patients (15%).

All operations were conducted using optical magnification and bipolar coagulation, as described previously (21). 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 (22). 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

A total of 300 entire thyroid glands were available for histopathological examination. 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 (23). 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 on evidence of tumor extension beyond the basement membrane, demonstration of lymphatic or vascular invasion on histopathology, or a combination thereof. 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. A diagnosis of nodal metastasis required pathological confirmation. In the absence of a tissue diagnosis from distant organs, unequivocal evidence on ultrasonography, computed tomography, magnetic resonance imaging, positron emission tomography, or a combination thereof, was considered sufficient proof of distant metastasis.

Data analysis

To correct for the preferential referral of patients with more advanced disease to specialist centers (24), the clinicopathological data, many of which are interrelated, were stratified by largest primary tumor diameter (5 mm increments), number of lymph node metastases (5 to 10 node increments), and various brackets of pretherapeutic basal calcitonin and CEA levels, considering the number of patients available. Spearman's rank correlation coefficient was calculated to evaluate the overall suitability of the respective biomarkers as indicators of primary tumor diameter and lymph node metastases, with a higher correlation coefficient denoting superiority. These correlation coefficients were corrected for the number of observations (adjusted Spearman's correlation) to eliminate the possibility that greater correlation coefficients may have been caused by the availability of more data for the respective biomarker. Spearman's correlation coefficients were squared (r^2) to determine the variance in primary tumor diameter and the number of lymph node metastases explained by the respective biomarker brackets. 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. This conservative approach yielded minimum estimates of compartmental involvement.

Results

Biomarker levels by primary tumor diameter and number of lymph node metastases

With every increment in primary tumor diameter, basal calcitonin, stimulated peak calcitonin, and CEA serum levels increased progressively, as did the number of lymph node metastases (Table 1). When the divergent numbers of patients in each biomarker group were corrected for (adjusted Spearman's rho), basal calcitonin ($r = 0.83$; $P < 0.001$) and CEA ($r = 0.84$; $P < 0.001$) serum levels correlated most closely with primary tumor diameter, ex-

TABLE 1. Calcitonin and CEA levels and lymph node metastases by tumor diameter

	Basal calcitonin (pg/ml) (<5–10 pg/ml)[a]		Stimulated peak calcitonin (pg/ml) (<5–10 pg/ml)[a,b]		CEA (ng/ml) (<4.6 ng/ml)[c]		Lymph node metastases, n	
	n[d]	Mean (95% CI)	n[d]	Mean (95% CI)	n[d]	Mean (95% CI)	n[d]	Mean (95% CI)
Largest tumor diameter (mm)								
0.1–5	87	69 (32; 105)	59	749 (308; 1,191)	53	2.5 (1.9; 3.2)	89	0.8 (0.1; 1.5)
5.1–10	52	421 (100; 742)	30	5,034 (1,795; 8,392)	34	10.4 (5.2; 15.7)	55	1.4 (0.3; 2.4)
10.1–15	44	1,793 (562; 3,024)	16	7,945 (2,795; 13,095)	30	39.9 (19.9; 59.8)	46	7.5 (3.6; 11.3)
15.1–20	29	4,819 (1,324; 8,313)	14	25,361 (7,822; 42,901)	20	146.1 (32.7; 259.5)	29	11.2 (5.7; 16.8)
Greater than 20	67	9,918 (4,454; 15,382)	20	28,543 (17,389; 39,697)	47	175.3 (110.8; 239.8)	69	16.8 (10.5; 23.0)
Total	279	3,265 (1,830; 4,691)	139	8,993 (6,050; 11,936)	184	69.8 (47.1; 92.5)	288	6.9 (5.0; 8.7)
	n[d]	r (*P*)	n[d]	r (*P*)	n[d]	r (*P*)	n[d]	r (*P*)
Spearman's rho								
Crude	279	0.83 (<0.001)	139	0.78 (<0.001)	184	0.80 (<0.001)	288	0.52 (<0.001)
Adjusted[e]	106	0.83 (<0.001)	106	0.77 (<0.001)	106	0.84 (<0.001)	106	0.44 (<0.001)

CI, Confidence interval.

[a] Based on the ELSA-hCT assay (CIS Bio International; used between September 1995 and May 2004; normal range <10 pg/ml) and the Immulite 2000 calcitonin assay (Diagnostic Products Corp.; used after May 2004; normal range <5 pg/ml for women and <8.4 pg/ml for men), respectively.

[b] Pentagastrin (0.5 μg) per kilogram body weight (Peptavlon; Laboratoires SERB).

[c] Based on the Elecsys assay (Roche Diagnostics; normal range <4.6 ng/ml).

[d] Number of patients in the respective tumor diameter bracket (base are 288 patients with information on largest primary tumor diameter).

[e] Based on only those patients with information on preoperative basal calcitonin, stimulated calcitonin, and CEA levels and the number of lymph node metastases.

TABLE 2. Calcitonin and CEA levels and tumor diameter by lymph node metastases

	Basal calcitonin (pg/ml) (<5–10 pg/ml)[a]		Stimulated peak calcitonin (pg/ml) (<5–10 pg/ml)[a,b]		CEA (ng/ml) (<4.6 ng/ml)[c]		Largest primary tumor diameter (mm)	
	n[d]	Mean (95% CI)	n[d]	Mean (95% CI)	n[d]	Mean (95% CI)	n[d]	Mean (95% CI)
Lymph node metastases, n								
0	168	559 (309; 809)	103	5,381 (2,971; 7,390)	107	28.0 (14.2; 41.7)	174	9.6 (8.1; 11.2)
1–5	40	1,664 (332; 2,997)	16	12,248 (2,957; 21,538)	27	30.8 (11.0; 50.6)	39	18.9 (12.5; 25.3)
6–10	19	7,568 (0; 16,842)	7	8,534 (2,557; 14,510)	16	133.2 (0; 296.6)	19	21.8 (14.6; 29.0)
11–20	24	11,110 (500; 21,720)	8	28,305 (0; 61,105)	16	146.6 (39.7; 253.5)	22	23.0 (14.9; 31.1)
21–30	16	11,738 (1,428; 22,049)	4	22,346 (0; 69,659)	11	143.6 (33.2; 254.0)	14	32.6 (23.2; 42.0)
Greater than 30	24	21,486 (6,730; 36,243)	4	40,374 (0; 81,395)	17	248.8 (124.4; 373.2)	20	29.4 (22.5; 36.3)
Total	291	4,379 (2,614; 6,145)	142	8,920 (6,037; 11,803)	194	72.7 (50.4; 95.1)	288	15.2 (13.4; 17.0)
	n[d]	r (*P*)	n[d]	r (*P*)	n[d]	r (*P*)	n[d]	r (*P*)
Spearman's rho								
Crude	291	0.66 (<0.001)	142	0.43 (<0.001)	194	0.54 (<0.001)	288	0.53 (<0.001)
Adjusted[e]	106	0.59 (<0.001)	106	0.40 (<0.001)	106	0.47 (<0.001)	106	0.45 (<0.001)

CI, Confidence interval.

[a] Based on the ELSA-hCT assay (CIS Bio International; used between September 1995 and May 2004; normal range <10 pg/ml) and the Immulite 2000 calcitonin assay (Diagnostic Products Corporation; used after May 2004; normal range <5 pg/ml for women and <8.4 pg/ml for men), respectively.

[b] Pentagastrin (0.5 μg) per kilogram body weight (Peptavlon; Laboratoires SERB).

[c] Based on the Elecsys assay (Roche Diagnostics; normal range <4.6 ng/ml).

[d] Number of patients in the respective lymph node bracket (base are all 300 study patients).

[e] Based on only those patients with information on preoperative basal calcitonin, stimulated calcitonin, and CEA levels and largest primary tumor diameter.

plaining 69–71% of the variance in primary tumor size, followed by stimulated peak calcitonin levels (r = 0.77; $P < 0.001$).

Greater numbers of lymph node metastases were also connected to higher stratified serum levels of basal calcitonin, stimulated peak calcitonin and CEA, and larger primary tumor diameters (Table 2). These correlations were not as firm as those for primary tumor diameter: strongest for basal calcitonin (r = 0.59; $P < 0.001$), followed by CEA (r = 0.47; $P < 0.001$) and primary tumor diameter (r = 0.45; $P < 0.001$) and weakest for stimulated peak calcitonin levels (r = 0.40; $P < 0.001$). None of the biomarker levels accounted for more than 44% of the variance in the number of lymph node metastases.

Tumor size, lymph nodes, and biochemical cure by biomarker levels

Higher stratified basal calcitonin and CEA serum levels reflected greater numbers of lymph node metastases, increasingly precluding postoperative normalization of calcitonin levels. For patients failing to achieve biochemical cure in the absence of distant metastases, the numbers of lymph node metastases given may represent underestimates because some metastases may have been left behind in undissected lymph node compartments or far-off regions of dissected lymph node compartments. Yet a few node-negative tumors were seen with excessive basal calcitonin and CEA levels. Unlike basal calcitonin levels of 20 pg/ml or less (Table 3), normal CEA levels cannot exclude lymph node metastases, nor do they guarantee biochemical cure (Table 4).

Involvement of lymph node compartments and distant metastasis by basal calcitonin

With every increment of stratified basal calcitonin levels, there was a successive involvement of the ipsilateral neck, contralateral neck, and upper mediastinal lymph node compartments (Table 5). Lymph node metastases were present in the ipsilateral (central and lateral) neck, contralateral central neck, contralateral lateral neck, and upper mediastinum beyond basal calcitonin thresholds of 20, 50, 200, and 500 pg/ml, respectively. Similar rates of involvement were found in the central and lateral compartments of the ipsilateral neck, which were higher than those in the upper mediastinum (Table 5). Distant metastases were not seen below a basal calcitonin threshold of 500 pg/ml.

Conceivably, occult lymph node metastases might have been left behind in undissected lymph node compartments so that the actual rates of involvement may have been higher than the minimum estimates for the 268 patients in Table 5. Obviously, this was not a frequent event because only 4.6 and 9.7% of the 50 (19%) and 57 (21%) among the 268 patients who did not undergo a lateral lymph node dissection ipsilaterally or contralaterally showed no normalization of postoperative calcitonin levels. Intriguingly, patients who did

TABLE 3. Tumor diameter and lymph node metastases by basal calcitonin level

Basal calcitonin level (pg/ml)		Largest primary tumor diameter (mm)[a]		Number of involved lymph nodes		Number of removed lymph nodes		Biochemical cure[b]
(<5–10 pg/ml)[c]	n[d]	Mean (95% CI)	Range	Mean (95% CI)	Range	Mean (95% CI)	Range	n (%)[b]
10.1–20	23	3.3 (2.4; 4.2)	1–8	0	0	8.3 (4.9; 11.7)	1–31	22 (100)
20.1–50	35	4.5 (3.6; 5.4)	1–12	0.5 (0; 1.2)	0–12	36.1 (25.0; 47.1)	1–105	31 (100)
50.1–100	23	6.2 (4.5; 7.8)	1.3–20	0.3 (0; 0.6)	0–3	54.1 (38.3; 69.9)	3–130	19 (100)
100.1–200	26	8.9 (6.7; 11.0)	2–25	1.5 (0; 2.9)	0–17	49.5 (36.8; 62.2)	1–128	17 (81)
200.1–500	29	11.4 (9.7; 13.0)	5–21	2.3 (0.9; 3.8)	0–16	64.2 (52.4; 75.9)	11–137	21 (81)
500.1–1,000	34	20.4 (15.0; 25.9)	1.5–70	7.5 (3.9; 11.1)	0–41	69.8 (58.5; 81.2)	24–158	14 (50)
1,000.1–2,000	34	24.0 (19.2; 28.8)	2–60	9.3 (4.1; 14.6)	0–56	68.2 (58.8; 77.6)	4–118	10 (40)
2,000.1–10,000	39	27.5 (23.3; 31.7)	9–55	15.9 (10.6; 21.3)	0–68	64.1 (56.1; 72.1)	8–128	6 (18)
Greater than 10,000	25	34.9 (28.3; 41.6)	12–65	35.3 (21.3; 49.4)	0–167[e]	71.3 (52.9; 89.8)	6–209	0 (0)
Total	268	15.9 (14.2; 17.7)	1–70	8.2 (6.2; 10.3)	0–167	55.3 (51.0; 59.6)	1–209	140 (61)

CI, Confidence interval.

[a] Based on 256 patients with information on primary tumor diameter.

[b] Normalization of postoperative calcitonin levels based on 231 patients with pertinent information at a mean follow-up of 54.4 months.

[c] Based on the ELSA-hCT assay (CIS Bio International; used between September 1995 and May 2004; normal range <10 pg/ml) and the Immulite 2000 calcitonin assay (Diagnostic Products Corp.; used after May 2004; normal range <5 pg/ml for women and <8.4 pg/ml for men), respectively.

[d] Number of patients in the respective calcitonin bracket (base are 268 patients after exclusion of 23 patients with basal calcitonin levels ≤10 pg/ml and nine patients whose preoperative calcitonin levels were not determined with the ELSA-hCT or Immulite 2000 calcitonin assay).

[e] No nodes involved among 63 removed nodes (basal calcitonin level 17,511 pg/ml).

not reach biochemical cure postoperatively had an additional 20 lymph nodes cleared compared with patients who were biochemically cured (means of 68.4 *vs.* 48.0 removed nodes; $P < 0.001$). Despite the clearance of additional lymph node metastases, extensive lymph node dissection more and more was unable to secure biochemical cure in the presence of higher preoperative biomarker serum levels (Tables 3 and 4), presumably because the prevalence of occult systemic disease was also increasing with these levels.

Surgical morbidity

Transient hypoparathyroidism was noted in 22% (66 patients) and transient recurrent laryngeal nerve palsy (all unilateral) in 5.0% (15 patients) of the 300 patients. Cervical reoperations were required for major postoperative hemorrhage in 3.3% (10 patients), lymphatic fistula in 2.3% (seven patients), and major wound infections in 1.0% (three patients).

Permanent complications included hypoparathyroidism in 5.7% (17 patients); recurrent laryngeal nerve palsy (all

TABLE 4. Tumor diameter and lymph node metastases by CEA level

CEA level (ng/ml)		Largest primary tumor diameter (mm)[a]		Number of involved lymph nodes		Number of removed lymph nodes		Biochemical cure[b]
(<4.6 ng/ml)[c]	n[d]	Mean (95% CI)	Range	Mean (95% CI)	Range	Mean (95% CI)	Range	n (%)[b]
Less than 4.6	68	5.5 (3.7; 7.2)	0.3–55	1.1 (0.2; 2.0)	0–20[e]	35.7 (27.0; 44.3)	1–129	60 (95)
4.6–10	25	9.5 (6.5; 12.5)	1.2–25	5.2 (0.2; 10.1)	0–56	55.8 (44.7; 66.9)	2–105	16 (73)
10.1–20	22	19.3 (9.3; 29.3)	5–110	5.0 (1.4; 8.6)	0–24	62.8 (48.4; 77.3)	5–131	10 (56)
20.1–50	29	19.1 (14.7; 24.4)	8–65	5.1 (1.7; 8.5)	0–38	66.7 (56.0; 77.4)	27–158	9 (47)
50.1–100	18	22.6 (16.4; 28.8)	9–60	23.2 (3.6; 42.9)	0–167	77.1 (56.4; 97.9)	31–209	2 (15)
100.1–300	16	32.5 (25.3; 39.8)	13–55	20.4 (10.7; 30.1)	0–53	63.3 (47.6; 79.0)	7–128	1 (8)
Greater than 300	16	37.9 (28.0; 47.7)	19–70	25.5 (12.5; 38.5)	0–81[f]	58.9 (42.0; 75.8)	6–134	2 (13)
Total	194	15.8 (13.5; 18.1)	0.3–110	8.3 (5.7; 10.9)	0–167	54.0 (49.0; 59.1)	1–209	99 (61)

CI, Confidence interval.

[a] Based on 184 patients with information on primary tumor diameter.

[b] Normalization of postoperative calcitonin levels based on 163 patients with pertinent information at a mean follow-up of 54.4 months.

[c] Based on the Elecsys assay (Roche Diagnostics; normal range <4.6 ng/ml).

[d] Number of patients in the respective CEA level bracket (base are 194 patients with information on CEA levels).

[e] One (CEA levels 1.0–4.4 ng/ml; five patients), two (CEA level 3.4 ng/ml), three (CEA level 2.3 ng/ml), four (CEA level 2.6 ng/ml), seven (CEA level 1.0 ng/ml), 14 (CEA level 3.9 ng/ml), 17 (CEA level 1.7 ng/ml), and 20 positive nodes (CEA level 3.0 ng/ml).

[f] No nodes involved among 29, 36, and 49 removed nodes (CEA levels 445.7, 383.3, and 327.0 ng/ml, respectively).

TABLE 5. Frequency and pattern of lymph node metastases by serum level of basal calcitonin

Basal calcitonin level		Lymph node metastasis[a]	Involvement of lymph node compartments					
			Ipsilateral neck		Contralateral neck		Upper mediastinum	Distant metastasis
(<5–10 pg/ml)[b]	n[c]	n (%)	Central n (%)	Lateral n (%)[d,e]	Central n (%)	Lateral n (%)[e,f]	n (%)[e,g]	n (%)
10.1–20	23	0	0	0	0	0	0	0
20.1–50	35	4 (11)	3 (9)	3 (9)	0	0	0	0
50.1–100	23	4 (17)	2 (9)	3 (13)	1 (4)[h]	0	0	0
100.1–200	26	9 (35)	7 (27)	4 (15)	1 (4)	0	0	0
200.1–500	29	13 (45)	10 (34)	11 (38)	3 (10)	4 (14)[i]	0	0
500.1–1,000	34	20 (59)	16 (47)	17 (50)	7 (21)	4 (12)	4 (12)[j]	2 (6)
1,000.1–2,000	34	18 (53)	13 (38)	14 (41)	6 (18)	6 (18)	4 (12)	5 (15)
2,000.1–10,000	39	31 (79)	27 (69)	29 (74)	14 (36)	17 (44)	5 (13)	6 (15)
Greater than 10,000	25	24 (96)	20 (80)	24 (96)	19 (76)	20 (80)	13 (52)	18 (72)
Total	268	123 (46)	98 (37)	105 (39)	51 (19)	51 (19)	26 (10)	31 (12)

[a] Any location; [b] based on the ELSA-hCT assay (CIS Bio International; used between September 1995 and May 2004; normal range <10 pg/ml) and the Immulite 2000 calcitonin assay (Diagnostic Products Corp.; used after May 2004; normal range <5 pg/ml for women and <8.4 pg/ml for men), respectively; [c] number of patients in the respective calcitonin bracket (base are 268 patients after exclusion of 23 patients with basal calcitonin levels ≤10 pg/ml and nine patients whose preoperative calcitonin levels were not determined with the ELSA-hCT or Immulite 2000 calcitonin assay); [d] based on 218 patients with systematic lateral lymph node dissection in the ipsilateral neck; [e] counting undissected compartments as node negative; [f] based on 211 patients with systematic lateral lymph node dissection in the contralateral neck; [g] based on 42 patients with transsternal systematic lymph node dissection in the upper mediastinum; [h] level 91.4 pg/ml; [i] minimum level 205 pg/ml; [j] minimum level 515 pg/ml; miliary lung metastases (histologically confirmed).

unilateral) in 2.3% (seven patients); unilateral accessory nerve palsy coupled with Horner's syndrome in 0.3% (one patient); and unilateral phrenic nerve palsy in 0.3% (one patient).

Many complications occurred as a function of the number of lymph nodes removed: Postoperative hypoparathyroidism (means of 58 and 69 dissected nodes for transient and permanent hypoparathyroidism *vs.* 49 dissected nodes; $P = 0.031$); postoperative hemorrhage (means of 75 *vs.* 51 dissected nodes; $P = 0.032$); postoperative wound infection (means of 130 *vs.* 51 dissected nodes; $P < 0.001$); and lymphatic fistula (means of 82 *vs.* 52 dissected nodes; $P = 0.045$). No such dependency was observed for recurrent laryngeal nerve palsy (means of 53 and 67 dissected nodes for transient and permanent recurrent laryngeal nerve palsy *vs.* 52 dissected node; $P = 0.57$).

For these complications to happen, a minimum number of lymph nodes obviously needed to have been cleared: three and 11 nodes for transient and permanent hypoparathyroidism; five and 35 nodes for transient and permanent recurrent laryngeal nerve palsy; 33 nodes for major postoperative hemorrhage; 45 nodes for major wound infections; 52 nodes for lymphatic fistula; 59 nodes for phrenic nerve palsy; and 64 nodes for axillary nerve palsy coupled with Horner's syndrome.

Discussion

Recognized for more than 25 yr as sensitive biomarkers for MTC, calcitonin and CEA serum levels have not comprehensively been evaluated in a head-to-head comparison for their clinical utility of indicating extent of disease and providing a biochemical stratification of pretherapeutic risk. Overall, stratified basal calcitonin and CEA were fairly powerful biomarkers, explaining some 70% of the variance in primary tumor size among previously untreated MTC patients. Although basal calcitonin levels were superior to CEA levels, especially at lower concentrations, none of the biomarkers explained more than 44% of the variance in the number of lymph node metastases. These data indicated that biomarker levels correlate more closely with tumor mass, especially when vascular supply and drainage of the tumor are excellent, as in node-negative MTC. In keeping with this assumption, lymph node metastases, which reside in a harsher environment with a worse perfusion, showed a markedly weaker correlation with basal calcitonin and CEA secretion. Apart from being better shielded from the effects of pentagastrin stimulation, lymph node metastases, having acquired additional somatic mutations for lymphatic spread, may also be less differentiated than their corresponding primaries (17). All these factors may have diminished the correlation between the biomarkers and the number of positive lymph nodes.

Clinical utility of pretherapeutic basal calcitonin levels

Although not perfect, pretherapeutic basal calcitonin serum levels do convey clinically useful information for previously untreated MTC patients. This biochemical information, enabling an assessment of the pretherapeutic risk of locoregional lymph node involvement and distant

metastases, should be integrated into clinical treatment plans. As shown in Table 5, all patients with basal calcitonin serum levels of 20 pg/ml or less may safely forgo systematic lymph node dissection (unless there is evidence to the contrary). In this setting, MTC is still uncommon, and the diagnosis is difficult to make because of the high prevalence of C cell hyperplasia (13, 15).

In a worst-case scenario, patients with confirmed MTC and basal calcitonin levels between greater than 20 and 50 pg/ml would need to undergo lymph node dissection only in the ipsilateral (central and lateral) neck (Table 5). Patients with basal calcitonin levels ranging from greater than 50 to 200 pg/ml and confirmed MTC would require a bilateral central and a lateral lymph node dissection in the ipsilateral neck. Beyond a basal calcitonin level of 200 pg/ml, central and lateral lymph node dissections would be necessary on both sides of the neck (Table 5). Mediastinal lymph node metastases were not seen with basal calcitonin levels of 500 pg/ml or less. Indeed, transsternal dissection of the mediastinal compartment should be reserved for confirmed mediastinal disease, which often heralds distant metastases (25).

Under worst-case assumptions, the majority of MTC patients with pretherapeutic basal calcitonin levels greater than 10 pg/ml, 161 of 268 patients in this series (60%), would require compartment-oriented surgery of the central and both lateral neck compartments because their preoperative basal calcitonin levels exceed 200 pg/ml. Systematic bilateral neck dissection may convert to normal at least half the patients with pretherapeutic basal calcitonin levels of 1000 pg/ml or less. Biochemical cure is still within reach below a basal calcitonin threshold of 10,000 pg/ml or less. Above that threshold, lymph node involvement is greater than 80% in the neck and greater than 50% in the upper mediastinum, with a greater than 70% prevalence of distant metastases (Table 5). In the presence of excessive calcitonin levels, these patients may benefit from systemic therapies as an adjunct to surgery.

The trade-off between biochemical cure and surgical morbidity

Lymph node metastases visualizing on cervical ultrasonography are believed to represent the tip of the iceberg of lymphatic tumor cell dissemination. The current principle, one positive node, one involved lymph node compartment, is founded on this concept. Occult lymph node metastases, escaping the most sophisticated imaging methods because of their miliary growth pattern, are a frequent source of recurrence if not cleared promptly. These recurrences require considerable time, effort, and resources to diagnose and treat.

Compartment-oriented surgery is believed to be more effective in normalizing calcitonin serum levels and achieving local control in the neck than selective dissection of enlarged lymph nodes. Systematic dissection of suspected or confirmed lymph node metastases yielded rates of lymph node involvement of 79–81% (ipsilateral neck) and 31–50% (contralateral neck) (26, 27). These rates were almost twice as high as our rates of 37–39% (ipsilateral neck) and 19% (contralateral neck) with compartment-oriented surgery triggered by increased serum biomarker levels. Even at centers specializing in thyroid cancer, cervical ultrasonography is fraught with a more than one third rate of false-negative findings (1), necessitating reoperations in the central neck at an excess risk of surgical morbidity. False-positive findings, triggering unnecessary neck dissections, were infrequent among previously untreated MTC patients (one of 22 patients, 5%) (1). Compared with dedicated centers, ultasonographic detection of neck lymph nodes, as practiced in the community, is believed to be inferior (28).

The price to be paid for the prospects of cure and protection from neck invasion by residual tumor (29) obviously is overtreatment. This is most evident in the lower calcitonin range in which lymph node involvement may be as low as 4–9%. As a corollary, all efforts must be made to keep surgical morbidity to a minimum. These efforts should include the use of nerve-monitoring devices, bipolar forceps and optical magnification, *in situ* preservation, or autografting of parathyroid glands as necessary. Compartment-oriented surgery can be accomplished safely with a reasonable cosmetic result by heeding the rationale and principles of systematic lymph node dissection (26, 27, 30). The necessary standardization of, and experience with, this operative technique may be achieved more easily at dedicated surgical centers.

Current practice

A recent analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results database from 12 population-based cancer registries revealed room for improvement. As many as 41% of patients with stage IV medullary thyroid cancer, and sometimes even patients with stages II and III disease, underwent no cervical lymph node dissection (31). A detailed analysis of 46 reoperations for MTC from a specialist center revealed that residual tumor was located in the central neck compartment in 22%, in the lateral neck compartment in 64%, and in the anterior mediastinum in 14% (32). In patients who underwent an initial total thyroidectomy and central neck dissection, residual MTC was found in the lateral neck in 70% and in the central neck and the mediastinum in 15% each.

Clinical implications

Because there is no ideal detection method for lymph node metastases, a standardized approach to MTC, simplifying the logistics of cancer surveillance in the postoperative period, seems warranted. Such a standardized approach, based on a biochemical stratification of pretherapeutic risk, may be more cost effective than current practice, which is still marked by multiple reoperations for recurrent or persistent disease. To minimize surgical morbidity without compromising on cure, all MTC patients should be referred to specialist surgical centers in pursuit of the principle of first time right. The initial operation would then consist of total thyroidectomy coupled with systematic central and lateral lymph node dissection on both sides of the neck, unless basal calcitonin levels are 200 pg/ml or less. In that event, the lateral lymph node compartment of the contralateral neck could be spared. For recurrent tumor, a focused approach directed at single tumor deposits alone would be sufficient, with no need for extensive lymph node dissection in a scarred neck. The cost-effectiveness of this concept clearly hinges on the availability of, and patient access to, surgeons having the special skills of clearing all neck nodes at minimal surgical morbidity. Further studies are necessary to confirm the viability of this biomarker-based, risk-stratified approach to a cancer characterized by a high disease burden and the absence of effective treatment options other than surgery.

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