

Prospects of Remission in Medullary Thyroid Carcinoma According to Basal Calcitonin Level

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Prediction of remission in medullary thyroid carcinoma (MTC) depends on histopathological information often unavailable before surgery. Simply requiring a venous blood sample, preoperative basal calcitonin levels may be a better indicator of remission. In this institutional series of 224 consecutive patients with MTC and elevated preoperative basal calcitonin levels, postoperative calcitonin levels normalized in 28 (62%) of 45 patients with node-negative MTC and in 18 (10%) of 177 patients with node-positive MTC. On multivariate analysis, preoperative basal calcitonin levels greater than 500 pg/ml best predicted the failure to achieve biochemical remission, followed by nodal metastasis and reoperative status. Cumulative rates of biochemical remission fell continuously

with rising serum basal calcitonin in node-negative patients. Node-positive patients did not achieve biochemical remission when their preoperative basal calcitonin levels exceeded 3000 pg/ml. Nodal metastasis started emerging at basal calcitonin levels of 10–40 pg/ml (normal range, <10 pg/ml). Distant metastasis and extrathyroidal growth began appearing in patients with node-positive MTC at basal calcitonin levels of 150–400 pg/ml. There were no differences between patients with sporadic and hereditary MTC after adjusting for multiple testing. Preoperative basal calcitonin levels may thus help individualize the extent of surgery and postoperative follow-up intervals for MTC. (*J Clin Endocrinol Metab* 90: 2029–2034, 2005)

FAILURE OF CALCITONIN levels to normalize after surgery, or biochemical remission, is a common phenomenon in medullary thyroid carcinoma (MTC) indicative of residual tumor deposits (1). Postoperative normalization of serum calcitonin predicts a survival rate of 97.7% at 10 yr (2). Rates of postoperative normalization of serum calcitonin can vary considerably between surgical centers due to differences in the composition of patients, selection criteria for surgery, and extent of surgical intervention (1). When stratified by nodal status, rates of biochemical remission range from 83–95% for patients with node-negative MTC and from 21–32% for those with node-positive tumors (3–5).

The applicability of these heterogeneous aggregate data to individual patients is limited. Recently, quantitative lymph node analysis was shown to be a powerful tool of predicting postoperative normalization of serum calcitonin; involvement of 10 or more lymph nodes or more than two lymph node compartments almost precludes normalization of serum calcitonin (5, 6). Crucially dependent on systematic lymph node dissection and meticulous histopathological analysis, a patient's quantitative lymph node status is rarely available in the preoperative setting.

Tumor size and volume were found to significantly correlate with preoperative basal calcitonin levels (7, 8), a reflection of endogenous tumor burden (6). Simply requiring a venous blood sample, preoperative serum calcitonin may be more suitable than tumor size or quantitative lymph node

status (which require surgery and histopathological analysis) to appraise an individual MTC patient's prospects of biochemical remission. As of this writing, pertinent investigations on this topic are pending. The current study was set up to relate preoperative serum calcitonin levels and, for comparative purposes, primary tumor diameter to postoperative normalization of serum calcitonin and other histopathological variables.

Subjects and Methods

Patient selection

Between November 1994 and January 2004, a total of 384 consecutive patients with MTC were operated on at this institution, a tertiary surgical center with referrals from all over Germany. Informed consent was obtained before each surgical procedure that represented standard practice of care in accordance with the practice guidelines of the German Society of Surgery (9). Distant metastases were not an exclusion criterion. Before the introduction of the current solid two-site immunoradiometric calcitonin assay (ELSA-hCT, CIS bio International, Gif-sur-Yvette, France) at our institution in September 1995, 83 patients had been tested with another calcitonin assay and hence are not part of the study. Of the remaining 301 patients, 49 patients displayed basal serum calcitonin levels less than 10 pg/ml (or 10 ng/liter in *Système International* units). This is the upper normal limit of this assay, as verified in 83 normal volunteers, aged 7–60 yr (10, 11). These 49 patients were not included in the study because of the need for a homogeneous population of patients with elevated preoperative basal serum calcitonin levels, leaving a total of 252 patients.

Calcitonin testing

Normalization of serum calcitonin was assumed when the upper normal limit of 10 pg/ml (or 10 ng/liter in *Système International* units) was not exceeded basally or with pentagastrin stimulation. Patients who achieved normalization of their serum calcitonin levels, or biochemical remission, after surgery also needed to have had pentagastrin stimulation to enable proper evaluation of surgical outcome. This criterion

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was not met by 28 patients who, therefore, were excluded. Calcitonin stimulation was performed after obtaining informed consent through iv bolus injection of pentagastrin (0.5 $\mu\text{g}/\text{kg}$ body weight; Pentavlon, Laboratoires SERB, Paris, France); venous blood samples were drawn before the injection and 2 and 5 min thereafter. Of the remaining 224 study patients who had appropriate information on outcome, 97 underwent primary surgery, and 127 underwent reoperations. Reoperative patients differed from primary patients in primary tumor diameter (mean, 23.2 *vs.* 17.7 mm; $P < 0.001$) and nodal metastasis (96.0% *vs.* 58.8%; $P < 0.001$).

Extent of surgery

All surgical procedures were performed using optical magnification and bipolar coagulation, as described previously (12). At this institution, all 97 primary patients underwent total thyroidectomies, and 37 (29.1%) of the 127 reoperative patients underwent completion thyroidectomies, because the remainder (70.9%) had previously been thyroidectomized. In addition, 205 of these 224 patients (91.5%) underwent systematic dissections of the central lymph node compartment of the neck, which extends vertically from the hyoid bone to the thoracic inlet and horizontally between the carotid sheaths. The lateral lymph node compartments of the neck, which spread laterally from the carotid sheath to the trapezoid muscle and inferiorly from the subclavian vein to the hypoglossal nerve superiorly, were systematically dissected in 190 (84.8%; ipsilateral) and 183 patients (81.7%; contralateral). The mediastinal lymph node compartment, which comprises all nodes between the brachiocephalic vein and the tracheal bifurcation within the upper anterior and posterior mediastinum, was systematically dissected in 66 (29.5%) of the 224 study patients. Freedom from nodal metastasis was only assumed in the 19 patients (8.5%) who did not have lymph node compartments dissected when both basal and stimulated serum calcitonin levels normalized postoperatively.

Pathological examination and tumor staging

A total of 224 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 previously (13). 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. Tumor size, which had been ascertained by direct measurements of the surgical thyroid specimens, was taken from the pathology reports. Although a diagnosis of nodal metastasis usually required pathological confirmation, this need was waived for distant metastasis when there was such unequivocal evidence on ultrasonography (liver), computerized tomography, magnetic resonance imaging, positron emission tomography, scintiscan, or a combination thereof.

Statistical analysis

Categorical and continuous data were tested on univariate analysis with the two-tailed Fisher exact test and the two-tailed exact Mann-Whitney-Wilcoxon rank-sum test, respectively. For univariate and multivariate analyses of cumulative risks, the Kaplan-Meier method (log-rank test) (14) and the Cox proportional hazards model (15) were used. The level of significance was set at 0.05.

Results

Demographics and histopathological features of the study population

Patients with postoperative normalization of serum calcitonin differed significantly ($P < 0.001$) from those with persistent hypercalcitoninemia in terms of operative status (primary surgery *vs.* reoperation), preoperative basal serum calcitonin, primary tumor diameter, extrathyroidal growth, nodal metastasis, number of positive lymph nodes, and distant metastasis, as ascertained at the time of operation (Table 1). Both groups were comparable with regard to gender, age at first diagnosis of MTC, REarranged during Transfection (RET) gene carrier status, *i.e.* heredity of MTC, preoperative stimulated serum calcitonin, and number of sampled lymph

TABLE 1. Patient demographics and histopathological features

Variable	Postoperative calcitonin normalization		P^a
	Accomplished (n = 46)	Failed (n = 178)	
Patient age at first diagnosis, yr [mean (95% CI)]	45.5 (40.5, 50.5)	45.0 (42.7, 47.4)	0.80
Gender (% male)	47.8	48.3	>0.99
RET gene carrier (%)	37.0	29.2	0.21
Primary surgery (%)	76.1	34.8	<0.001
Preoperative basal calcitonin, pg/ml (ng/liter) [mean (95% CI)]	401 (176, 625)	6,170 (3,132, 9,208)	<0.001
Preoperative stimulated calcitonin, pg/ml (ng/liter) [mean (95% CI)] ^b	2,975 (1,440, 4,510)	9,494 (5,262, 13,725)	0.27
Primary tumor diameter, mm [mean (95% CI)] ^c	12.9 (9.2, 16.6)	23.0 (20.6, 25.4)	<0.001
Extrathyroidal growth (%) ^d	2.2	30.5	<0.001
Nodal metastasis (%) ^e	39.1	90.3	<0.001
Positive lymph nodes [mean (95% CI)] ^d	1.5 (0.8, 2.2)	12.0 (9.3, 14.6)	<0.001
Sampled lymph nodes [mean (95% CI)] ^d	47.0 (40.2, 53.9)	52.2 (47.4, 57.0)	0.46
Distant metastasis (%) ^f	2.2	26.4	<0.001

RET, REarranged during Transfection; CI, confidence interval.

^a By two-tailed exact Mann-Whitney-Wilcoxon rank-sum test and Fisher exact test, respectively.

^b Based on 77 patients.

^c Information missing for 37 patients.

^d Information missing for 10 patients.

^e Information missing for two patients.

^f As ascertained at the time of operation.

nodes. Of the seven significant variables, only operative status, basal serum calcitonin, and occasionally nodal status can be reliably ascertained in the preoperative setting.

Multivariate logistic regression on failure to achieve biochemical remission

Variables identified as significant on univariate analysis (Table 1) were then entered into multivariate logistic regression models, with failure to achieve postoperative biochemical remission being the dependent variable (Table 2). Both models included categorized preoperative basal calcitonin levels, operative status (reoperation *vs.* primary operation), categorized primary tumor diameter, and nodal status (presence *vs.* absence of nodal metastasis). The full model included, in addition, extrathyroidal growth and distant metastasis, as ascertained at the time of operation. As shown in Table 1, both extrathyroidal growth and distant metastasis at the time of operation were closely associated with the failure of postoperative calcitonin levels to normalize, leading to an unstable full model (Table 2, *center column*). By this token and because of the nonsignificance of the two affected variables, extrathyroidal growth and distant metastasis, as ascertained at the time of operation, were not included in the reduced model (Table 2, *right column*). Regardless of the model considered, preoperative basal calcitonin levels above 500 pg/ml, presence of nodal metastasis, and reoperative status, but not categorized primary tumor diameter, indicated the failure to achieve biochemical remission after surgery. The magnitude of this effect, expressed as the odds ratio, was greatest for preoperative basal calcitonin levels of more than 500 pg/ml (odds ratio, 6.0–8.0 to 11.2–19.7), followed by nodal metastasis (odds ratio, 3.6–5.9) and reoperative status (odds ratio, 4.2–5.1).

Unlike average rates, cumulative frequency plots provide an estimate of the probability, or risk, that an individual has or does not have a given condition. Such cumulative frequency distributions can be used to calculate the numbers and percentages of values greater than or equal to the lower bound of a category (16).

TABLE 2. Multivariate logistic regression on failure to achieve biochemical remission postoperatively

Variable	n	Full model			Reduced model ^a		
		OR	(95% CI)	P	OR	(95% CI)	P
Preoperative basal calcitonin, pg/ml (ng/liter)							
10.1–100	37	1.0	Reference		1.0	Reference	
100.1–500	56	2.5	(0.8, 7.7)	0.10	3.0	(1.0, 9.3)	0.06
500.1–1000	29	6.0	(1.2, 29.4)	0.026	8.0	(1.6, 40.3)	0.011
>1000	65	11.2	(2.0, 62.0)	0.006	19.7	(3.6, 106.9)	0.0005
Reoperation <i>vs.</i> primary operation	96 <i>vs.</i> 91	5.1	(1.5, 17.7)	0.010	4.2	(1.2, 14.1)	0.022
Primary tumor diameter (mm)							
≤10	48	1.0	Reference		1.0	Reference	
10.1–20	67	2.6	(0.8, 8.2)	0.11	2.7	(0.8, 9.0)	0.11
>20	72	1.0	(0.3, 3.6)	0.95	1.1	(0.3, 4.3)	0.85
Presence <i>vs.</i> absence of nodal metastasis	142 <i>vs.</i> 45	3.6	(1.3, 10.0)	0.016	5.9	(2.2, 16.0)	0.0005
Extrathyroidal <i>vs.</i> intrathyroidal growth	40 <i>vs.</i> 147		— ^b	0.74 ^b			
Presence <i>vs.</i> absence of distant metastasis ^c	31 <i>vs.</i> 156		— ^b	0.80 ^b			

CI, Confidence interval; OR, odds ratio, serving as an estimate of the relative risk as this cannot be measured directly.

Failure to achieve biochemical remission is defined as failure of serum calcitonin to normalize [postoperative basal or stimulated calcitonin > 10 pg/ml (ng/liter)].

^a Excluding variables with skewed distribution (close association with failure of postoperative calcitonin to normalize).

^b Unstable model due to skewed distribution of variables (close association with failure of postoperative calcitonin to normalize).

^c As ascertained at the time of operation.

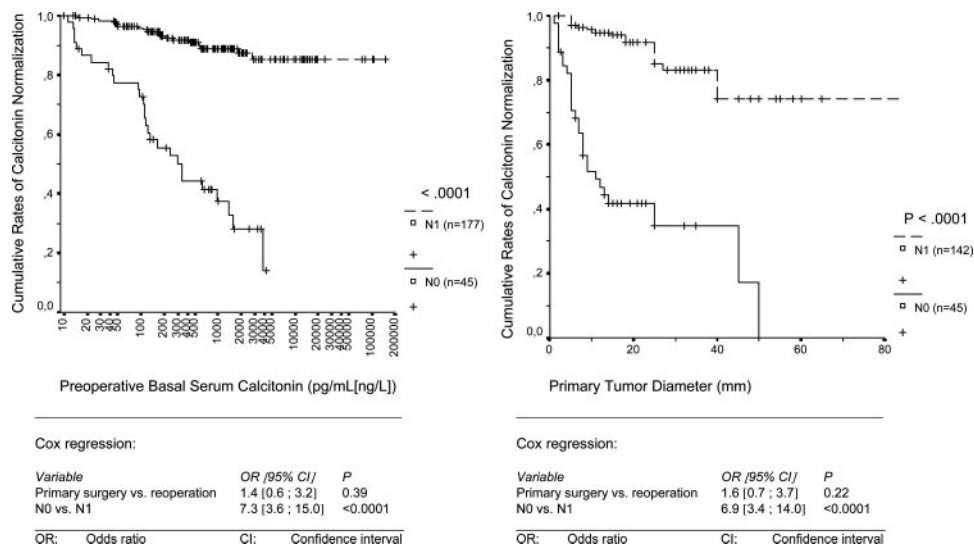
Cumulative normalization of serum calcitonin after surgery

In patients with node-negative MTC, cumulative rates of calcitonin normalization, or biochemical remission, fell continuously with rising preoperative basal serum calcitonin levels and primary tumor diameters (Fig. 1). The cumulative rate of biochemical remission in these patients declined to less than 50% when the preoperative basal serum calcitonin levels were higher than 300 pg/ml and primary tumor diameters measured more than 10 mm. In patients with node-positive MTC, these rates were no longer improved surgically beyond preoperative basal calcitonin levels of 3,000 pg/ml and primary tumor diameters of 40 mm. Overall, postoperative serum calcitonin levels normalized in 28 (62%) of the 45 patients with node-negative MTC and in 18 (10%) of 177 patients with node-positive MTC. On Cox regression (Fig. 1), operative status (primary operation *vs.* reoperation) had no significant additional effect on cumulative rates of calcitonin normalization. These rates were comparable for patients with sporadic and hereditary MTC (data not shown).

Cumulative risk of nodal metastasis

With rising preoperative basal serum calcitonin levels and primary tumor diameters, the cumulative risk of nodal metastasis surged, more rapidly in the reoperative than in the primary setting (Fig. 2). Nodal metastasis started emerging at preoperative basal serum calcitonin levels of 10 pg/ml (reoperative setting) and 40 pg/ml (primary setting) and at primary tumor diameters as small as 5 mm (primary and reoperative setting). Nodal metastasis was present in more than 50% of patients when preoperative basal serum calcitonin levels surpassed 500 pg/ml (reoperative setting) or 3,000 pg/ml (primary setting) and in tumors larger than 20 mm (primary and reoperative setting). Almost always present was nodal metastasis beyond preoperative basal serum calcitonin levels of 20,000 pg/ml (reoperative setting) and 100,000 pg/ml (primary setting), or beyond primary tumor diameters of 60 mm (primary and reoperative setting).

FIG. 1. Cumulative rates of postoperative calcitonin normalization.



The cumulative risk of nodal metastasis according to the preoperative basal calcitonin level was similar for patients with sporadic and hereditary MTC, but not according to primary tumor diameter ($P = 0.012$, by log-rank test; data not shown). Statistical significance, however, was lost after adjusting for multiple testing.

Cumulative risks of distant metastasis and extrathyroidal growth

In patients with node-negative MTC, it was not possible to confirm a single instance of distant metastasis or extrathyroidal growth by imaging or histopathology. Therefore, these patients were excluded from subsequent analyses. The curves for the cumulative risks of distant metastasis at the time of operation (Fig. 3) and extrathyroidal growth (Fig. 4) were almost congruent in patients with node-positive MTC. Relative to nodal metastasis (Fig. 2), the cumulative risks of distant metastasis and extrathyroidal growth also increased with rising preoperative basal serum calcitonin levels and primary tumor diameters, although somewhat later at much higher calcitonin levels and larger primary tumor diameters. Distant metastasis and extrathyroidal growth began appearing at preoperative basal serum calcitonin levels of 150 pg/ml (reoperative setting) and 400 pg/ml (primary setting) and at primary tumor diameters of 12–15 mm (primary and reoperative setting). The cumulative risks of distant metas-

tasis and extrathyroidal growth exceeded 50% at preoperative basal serum calcitonin levels of 5,000 pg/ml (reoperative setting) and 15,000 pg/ml (primary setting) and at primary tumor diameters of 50 mm (primary setting) and 60–65 mm (reoperative setting). Distant metastasis and extrathyroidal growth were almost always found beyond preoperative basal serum calcitonin levels of 20,000 pg/ml (reoperative setting) and 100,000 pg/ml (primary setting) or beyond primary tumor diameters of 60 mm (primary setting). For patients with sporadic and hereditary MTC, cumulative risks of distant metastasis and extrathyroidal growth did not differ significantly (data not shown).

Discussion

In sporadic and hereditary MTC, determination of serum calcitonin levels is the linchpin of both early diagnosis and ascertainment of postoperative outcome (biochemical remission). The rates of postoperative normalization of serum calcitonin may slightly overestimate actual remission rates, because 3.3% of MTC patients with initial biochemical remission will develop elevated serum calcitonin levels between 0.7 and 7.5 yr after surgery (17). Early diagnosis is more important than extensive surgery in improving remission rates in MTC. As a consequence, routine measurements of serum calcitonin have become an integral part of the clinical work-up for nodular goiter (18).

FIG. 2. Cumulative risk of nodal metastasis.

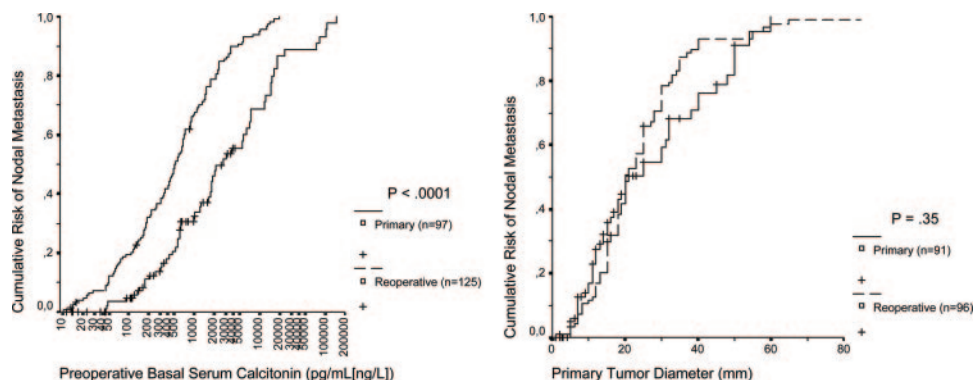
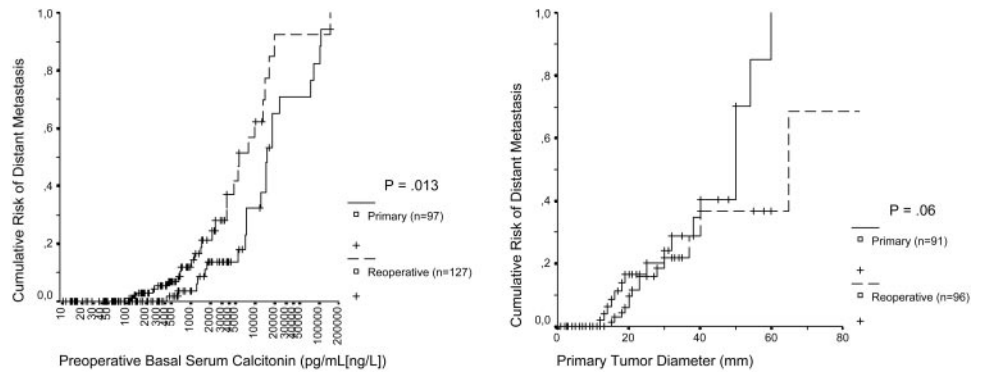


FIG. 3. Cumulative risk of distant metastasis in node-positive MTC (as ascertained at the time of operation).



Conversion of basal calcitonin measurements from the ELSA-hCT to the Nichols-Advantage assay

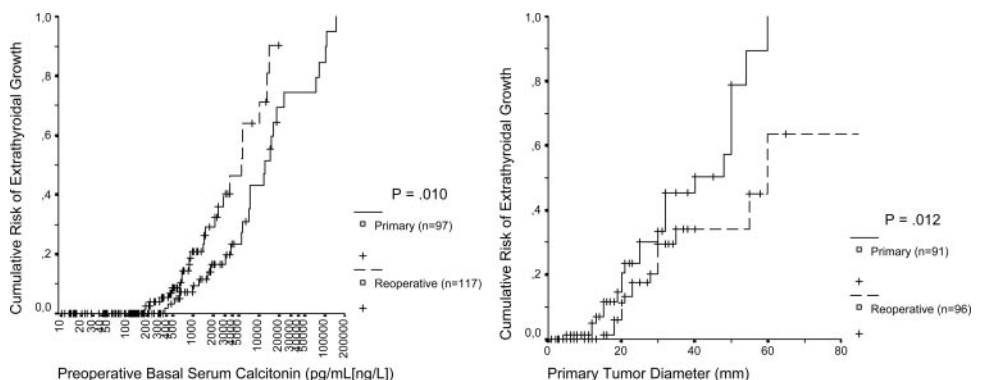
The persistence of elevated serum calcitonin levels after surgical intervention for MTC is associated with higher rates of local and distant recurrence and ultimately cause-specific mortality (19). The low physiological concentration of mature monomeric human calcitonin, polymeric forms, and its rapid degradation into immunoreactive fragments pose a considerable challenge for the development of immunoassays (20). Deviations from linear relationships are common for the ELSA-hCT immunoradiometric assay (CIS bio International), which is more commonly used in Europe, and the Nichols-Advantage immunochemiluminometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA), which is more prevalent in the United States. The correlation of calcitonin measurements between these two assays is excellent at a concentration of 1,000 pg/ml or less (100% between 0–30 pg/ml; 96% at ≤1,000 pg/ml). Above this level, at concentrations between 1,000 pg/ml and 20,000 pg/ml, the correlation declines to 75% (20).

Progression of MTC according to preoperative basal calcitonin

The correlation with biochemical remission in this study was better for preoperative basal than for pentagastrin-stimulated serum calcitonin levels. Pentagastrin is not available in the United States for routine use (21). Compared with data from the literature (3–5), our rates of postoperative calcitonin normalization (61% *vs.* 83–95% in node-negative MTC; 10% *vs.* 21–32% in node-positive MTC) were lower, presumably due to the inclusion of patients with elevated basal serum calcitonin, advanced MTC, and distant metastasis. The in-

clusion of these patients in our series ensured unbiased cumulative frequency estimates that applied to patients with sporadic and hereditary MTC alike. Of our 45 patients with node-negative MTC, 17 patients (38%) failed to reach normal serum calcitonin levels despite rather extensive surgery, a finding suggestive of occult distant metastasis. Nodal metastases were already present once basal calcitonin concentrations exceeded 10 pg/ml (upper normal limit of the assay) in the reoperative setting and 40 pg/ml in the primary setting. Characteristically, calcitonin levels were lower in the reoperative setting after removal of calcitonin-secreting tumor deposits at the primary operation. Such patients may have more aggressive disease and higher mortality rates than suggested by their relatively low preoperative calcitonin levels. In this setting, determination of serum carcinoembryonic antigen levels may be more meaningful. Primary tumor diameter, conversely, yielded more comparable curves for primary and reoperative MTC patients. The curves for the cumulative risks of distant metastasis and extrathyroidal growth were virtually congruent. Extrathyroidal growth is a recognized key risk factor of distant metastasis due to accession of the juxtathyroidal vascular system by continuity and indirectly through the passage of lymphatic tumor cells at the venous angle into the venous blood system (22). The observed rates of distant metastasis in this and other series obviously are minimum estimates, because some occult distant metastases may have escaped the various imaging modalities. More intensive imaging in MTC patients who have low preoperative basal calcitonin levels; more widespread use of sensitive, although invasive, techniques such as hepatic angiography (23), laparoscopic liver (24), thoracoscopic lung, and undirected (random) bone marrow (25) biopsies;

FIG. 4. Cumulative risk of extrathyroidal growth in node-positive MTC.



and a significant extension of the length of follow-up are likely to further improve the ascertainment rates of distant metastasis.

Clinical implications

In this investigation, preoperative basal calcitonin levels greater than 500 pg/ml better indicated the failure to achieve biochemical remission on multivariate analysis than reoperative status or nodal metastasis. At the French Institut Gustave-Roussy in Villejuif, selective venous catheterization with calcitonin measurements to localize occult metastatic disease is only performed in MTC patients whose postoperative calcitonin levels are below 500 pg/ml (26). Patients with calcitonin levels above this threshold are suspected to have distant metastases. In our 177 node-positive patients, biochemical remission was never accomplished when preoperative basal calcitonin levels exceeded 3,000 pg/ml [equivalent to 2,250 pg/ml with the Nichols-Advantage assay according to the Bieglmayer correction (20)]. Yen *et al.* (27) at the M. D. Anderson Cancer Center (Houston, TX) deem radiographic evidence of recurrent disease unlikely when the basal calcitonin level is 250 pg/ml or less with the Nichols-Advantage assay [equivalent to ≤ 260 pg/ml with the ELSA-hCT assay according to the Bieglmayer correction (20)]. With a view of individualizing patient care, more consideration should be given to the absolute level of preoperative basal serum calcitonin, not only in determining the extent of surgery, but also in scheduling the frequency of postoperative screening for local and distant recurrences.

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