Surgery Today
Jpn J Surg (1994) 24:112–121

SURGERY TODAY

Compartment-Oriented Microdissection of Regional Lymph Nodes in Medullary Thyroid Carcinoma

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Abstract: Lymph node metastases have been proven to be the main prognostic factor in medullary thyroid carcinoma (MTC). This retrospective study was undertaken to evaluate the efficiency of two surgical techniques of regional lymph node dissection with regard to the normalization of pentagastrin-stimulated serum calcitonin level and patient survival: selective lymphadenectomy, i.e., the excision of macroscopically or microscopically involved lymph nodes, versus a systematic lymphadenectomy performed by the new technique of a compartment-oriented microdissection. From 1970 to 1990, 82 patients with sporadic (n = 57) and hereditary (n = 25) MTC underwent a total of 142 operations including 63 selective lymphadenectomies and, since 1986, 35 systematic lymphadenectomies. The study revealed that in node-positive MTC the rate of interventions with a postoperative normalization of pentagastrin-stimulated serum calcitonin was higher after systematic lymphadenectomy (29.2%) than after selective lymphadenectomy (8.5%) ($P < 0.01$). The rate of patients undergoing repeat surgery due to a recurrence of MTC was 48% after selective lymphadenectomy and 10% after systematic lymphadenectomy. Survival was significantly better for patients after systematic versus selective lymphadenectomy ($P < 0.005$). This study thus emphasizes that systematic lymphadenectomy, using the technique of a compartment-oriented microdissection of cervicomediastinal lymph nodes, represents the preferred surgical treatment as well as the optimum technique in primary as well as secondary node-positive MTC.

Key Words: thyroid carcinoma, multiple endocrine neoplasia, lymphadenectomy, neck dissection

Introduction

Medullary thyroid carcinoma (MTC) represents a malignant neoplasia of the thyroid C-cell system belonging to the neuroendocrine, so-called amine precursor uptake decarboxylase (APUD) system[1]. In contrast to the follicular cell origin of papillary, follicular, and undifferentiated carcinoma of the thyroid gland, MTC occurs in a sporadic and a hereditary form,[2,3] and has been proven to be associated with a significant impairment of prognosis in node-positive patients.[4,5] Lymph node metastases are the determining event in both variants of MTC and may occur even in early tumor stages.[6]

Surgery is regarded as the treatment of choice in primary cases as well as in recurrent MTC due to the inability of sufficient radioiodine accumulation within the tumor tissue and insensitivity to external irradiation.[7,8] Since the establishment of MTC as a clinical and morphological entity of thyroid cancer,[9] it has been gradually recognized that surgical treatment has to be accomplished with a more radical approach in regard to the primary tumor and the regional lymph nodes than is applied to differentiated thyroid carcinoma.[10–14] These findings have been obtained by a careful analysis of the postoperative basal and pentagastrin-stimulated serum concentrations of calcitonin, which is the most important tumor cell-specific hormone product, and thus this method is considered to be a unique example of quality control in surgical oncology.[15–17]

Whereas total thyroidectomy has been widely accepted as an adequate surgical treatment of the primary tumor, the extent of surgery to the regional lymph nodes is still controversial. Some institutions prefer a more "selective" approach to regional lymph node metastases consisting in the removal of macroscopically or microscopically involved lymph nodes or groups of lymph nodes.[18,19] Others have recently reported a postoperative normalization of serum calcitonin levels that

Reprint requests to: H. Dralle
(Received for publication on June 29, 1992; accepted on May 7, 1993)

could only be achieved with "systematic" techniques of cervical lymphadenectomy.[10,13,14] In addition, in papillary thyroid carcinoma, systematic lymphadenectomy has turned out to be superior to the selective removal of lymph node metastases with regard to recurrence-free survival.[20]

With increased experience and the postoperative determination of calcitonin levels which has now become routine in our own surgical department, the operative strategy of lymphadenectomy in MTC has changed. From 1970 to 1986, a selective lymphadenectomy was performed on all node-positive patients. Since 1986, a systematic lymphadenectomy regimen has been established which consists of a tumor stage-correlated surgical removal of anatomically defined compartments of the central, lateral, and/or mediastinal lymph node regions.

Patients and Methods

Patients and Tumor Classification

From 1970 to 1990, 82 out of a total of 622 patients with thyroid carcinoma underwent either initial or secondary surgery for MTC at the Medizinische Hochschule Hannover (MHH). Twenty-five patients, belonging to 11 families, had hereditary MTC (23 patients with multiple endocrine neoplasia [MEN] 2A, 2 patients with MEN 2B) and 57 patients had sporadic MTC. All patients were followed up until December, 1991. The mean observation period was 5.1 years (range 0.2–59.3 years). Eighteen patients died from metastatic MTC while 2 patients died of non-tumor-related causes.

The probability of survival was analyzed using estimated survival curves,[21] employing the Mantel-Cox test and the generalized Wilcoxon test.[22] The histological classification of MTC was made according to the World Health Organization Typing of Thyroid Tumors (1988),[23] while the staging of primary tumors was done according to the TNM Classification for Malignant Tumors (1987).[24] Calcitonin testing after pentagastrin stimulation was performed by an intravenous bolus injection of 0.5 µg Gastrodiagnost/kg body weight with peripheral blood samples at 0, 2, and 5 min after injection. Plasma calcitonin was measured radioimmunologically by a commercial assay (RIA-mat calcitonin I, Mallinckrodt, Dietzenbach, Germany). Calcitonin concentrations greater than 0.3 ng/ml after pentagastrin stimulation in patients were considered to be consistent with recurrent or persistent MTC (no biochemical cure).

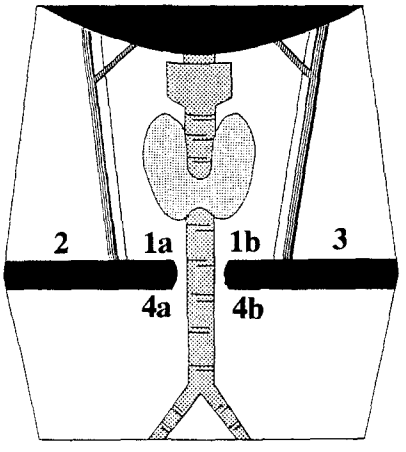


Fig. 1. Compartment definition of the cervicomediastinal lymph node system

Definition of Compartments and Type of Regional Lymph Node Metastases

On the basis of the surgical anatomy of the cervicomediastinal lymph node system, the following topographic definition of cervicomediastinal compartments has been used for the accomplishment and analysis of lymphadenectomy in MTC (Fig. 1):

Compartment 1: The cervicocentral lymph node system, right and left of the trachea, between the trachea and carotid sheath, and from the hyoid bone down to the brachiocephalic vein, including the submandibular lymph nodes.

Compartments 2 and 3: The right and left cervicolateral lymph node system between the carotid sheath and trapezoid muscle, from the subclavian vein up to the hypoglossic nerve, anterior, posterior and between the fascicles of the cervical plexus.

Compartment 4: Mediastinal lymph node system on both sides of the trachea from the left brachiocephalic vein down to the tracheal bifurcation within the anterior and posterior part of the mediastinum.

For analyses of the metastatic process in MTC, four types of cervicomediastinal lymph node metastases have been defined (Fig. 2):

Type A: MTC with unilateral lymph node metastases in the neck, confined to the perithyroidal, paratracheal, and/or cervicolateral lymph nodes.

Type B: MTC with bilateral lymph nodes in the neck, including a contralateral extension to the side of the primary tumor.

Type C: MTC with lymph node metastases on one side of the neck (including the paratracheal lymph nodes on

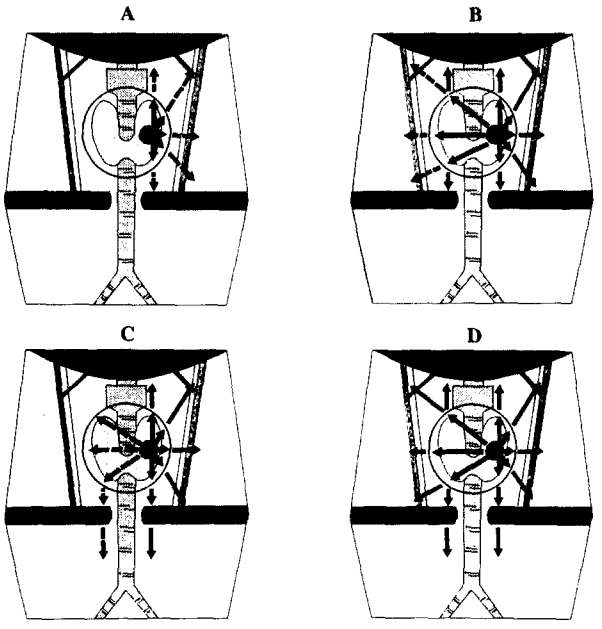


Fig. 2. Types of regional lymph node metastases in medullary thyroid carcinoma (*MTC*)

both sides) and within the upper mediastinum (below the left brachiocephalic vein) but without metastases to the contralateral cervicolateral compartment of the primary tumor.

Type D: MTC with lymph node metastases in all four cervicomediastinal compartments.

Surgical Technique

In all patients with MTC, a total thyroidectomy was performed. Since 1986, the surgical technique for a compartment-oriented microdissection of the cervicomediastinal lymph nodes has been developed. Until then, a selective lymphadenectomy approach had been used, i.e., the removal of the tumor with macroscopically involved lymph nodes or groups of lymph nodes together with the surrounding fat tissue. Since 1986, in the case of lymph node metastases, as evidenced by either macroscopy or an intraoperative frozen section, the entire lymph node compartment has been removed. The principle of this systematic lymphadenectomy is the en bloc microdissection of anatomically defined compartments containing lymph nodes, adipose, and connective tissue with the aid of a magnifying glass (2.5-fold magnification) and a bipolar coagulation pincette. All vital structures, muscles, vessels, and nerves are identified and preserved. The mediastinal compartment is removed by a transsternal approach. The number of lymph nodes excised and the number of tumor-involved lymph nodes are documented quantitatively by a histological analysis.

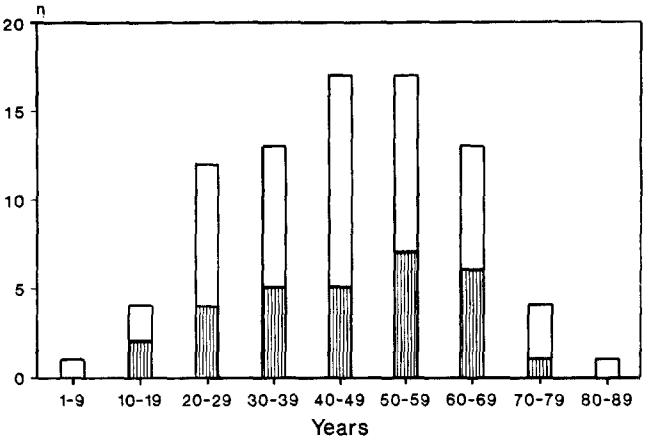


Fig. 3. Incidence of MTC by sex and age at the first surgical intervention (n = 82) *Hatched bars*, males; *white bars*, females

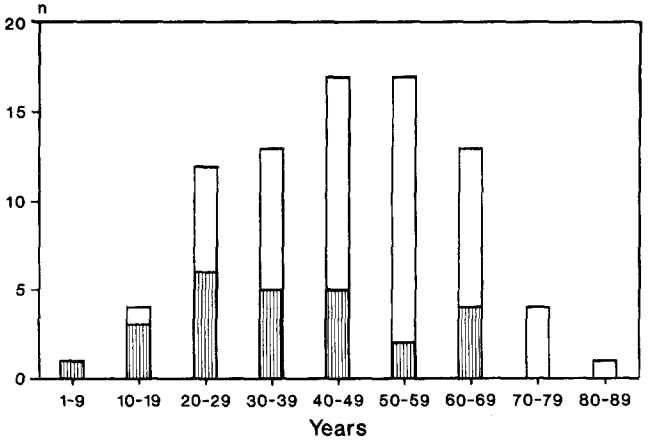


Fig. 4. Incidence of sporadic (n = 57) and hereditary (n = 25) MTC and age at the first surgical intervention. *Hatched bars*, hereditary; *white bars*, sporadic

Results

The patients' ages at the time of the first surgical intervention and the distribution of sporadic and hereditary cases are shown in Figs. 3 and 4. The overall female to male ratio was 1 : 1.8. The age of patients with hereditary MTC was significantly younger (mean age 36.4 years, range 6–69 years) than for patients with sporadic MTC (mean age 48.7 years, range 16–82 years).

In 20 out of the 57 patients with sporadic MTC, the preoperative basal calcitonin levels were correlated with the number of lymph node metastases as a result of the histological evaluation of the specimen after the total thyroidectomy and systematic lymphadenectomy. There was a positive correlation for these parameters (r = 0.64, Fig. 5).

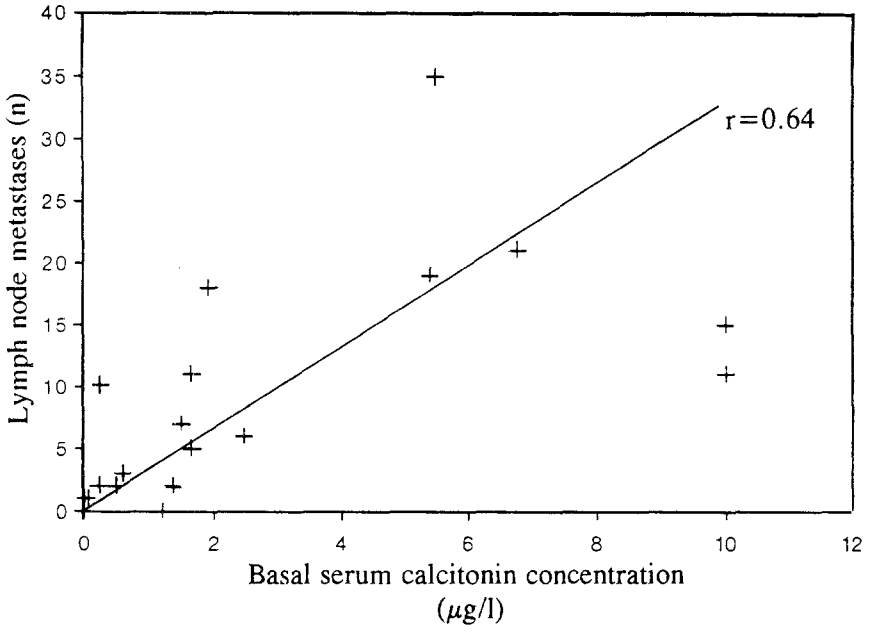


Fig. 5. Correlation of preoperative basal serum calcitonin concentration with the number of lymph node metastases in 20 patients with sporadic MTC. The definition of lymph node involvement included all surgical interventions due to MTC during the individual observation period of the patient

Lymph Node Status and Primary Tumor Size

In all 82 patients with MTC, the primary tumor size (largest diameter <1 cm, 1.0–1.9 cm, 2.0–3.9 cm, and >4 cm) and lymph node status according to the type of cervicomediastinal lymph node metastases were evaluated. As shown in Table 1, 55.2% of patients with hereditary MTC revealed no lymph node metastases during the entire observation period as compared to 22.8% of the patients with sporadic MTC. The percentage of patients with Type A lymph node metastases was 42.1% in patients with sporadic MTC and 20.0% in patients with hereditary MTC. Type B and D metastases were represented in similar percentages in sporadic and hereditary MTC. Type C, however, was demonstrated in 19.3% of patients with sporadic MTC compared to 4.0% of the patients with hereditary MTC.

Compartment-Correlated Quantitative Histological Analysis of Excised and Tumor-Involved Lymph Nodes

In the 20 patients mentioned above with sporadic MTC, which was surgically treated by systematic lymph-

Table 1. Lymph node status[a] and primary tumor size in patients with sporadic (n = 57) and hereditary (n = 25) medullary thyroid carcinoma

Primary tumor size (cm)[b]	n	No lymph node metastases (%)	Type A (%)	Type B (%)	Type C (%)	Type D (%)
Sporadic MTC						
<1	0	0	0	0	0	0
1.0–1.9	10	4	5	0	0	1
2.0–3.9	24	8	10	1	4	1
>4	23	1	9	3	7	3
Total	57	13 (22.8)	24 (42.1)	4 (7.0)	11 (19.3)	5 (8.8)
Hereditary MTC						
<1	10	7	2	0	1	0
1.0–1.9	5	5	0	0	0	0
2.0–3.9	8	3	3	2	0	0
>4	2	1	0	0	0	1
Total	25	16 (55.2)	5 (20.0)	2 (8.0)	1 (4.0)	1 (4.0)
Hereditary and sporadic MTC	82	29 (35.4)	29 (35.4)	6 (7.3)	12 (14.6)	6 (7.3)

MTC, medullary thyroid carcinoma.
[a] Lymph node status as defined according to the type of lymph node metastases. The definition of lymph node involvement included all surgical interventions due to MTC during the individual observation period of the patient.
[b] Largest diameter.

Table 2. Compartment-correlated quantitative histological analysis of excised and tumor-involved lymph nodes after systematic lymphadenectomy in 20 patients with sporadic medullary thyroid carcinoma

Compartment[a]	No. of patients	Mean positive LN (range)	Mean excised LN (range)
C1			
First operation	4	4.8 (0–9)	10.8 (6–18)
Recurrent operation	12	2.9 (0–12)	6.8 (3–16)
C2[b]			
first operation	4	10.8 (0–27)	22.8 (14–31)
Recurrent operation	10	2.0 (0–10)	15.9 (2–32)
C3[b]			
First operation	4	5.0 (0–8)	11.3 (4–17)
Recurrent operation	9	2.0 (0–5)	13.4 (6–26)
C4			
First operation	3	2.0 (0–3)	3.0 (3–4)
Recurrent operation[c]	3	4.7 (2–7)	11.3 (6–16)

LN, lymph nodes.
[a] See text for compartment definition.
[b] The quantitative analysis of lymph node metastases in C2 and C3 was based on five right lobe tumors but only three left lobe tumors.
[c] Recurrent cervical but first transsternal operation of compartment 4.

Table 3. Normal postoperative pentagastrin-stimulated serum calcitonin concentrations in 82 patients with sporadic and hereditary medullary thyroid carcinoma with regard to the type of lymph node metastases (LNM)

Surgical treatment	no LNM	Type A[a]	Type B	Type C	Type D
Only first operation ($n = 44$)[b]	20/23	7/13	0/3	0/2	0/3
With recurrent operation ($n = 38$)[c]	4/6[d]	2/16	0/3	2/10	0/3
Total ($n = 82$)	24/29 (82.7%)	9/29 (31.0%)	0/6	2/12 (16.7%)	0/6

[a] Type of lymph node metastases as defined in the text and as a result of the entire observation time of the individual patient.
[b] Patients with only the first tumor operation and no reoperation.
[c] Patients with a first and a recurrent operation.
[d] The indications for operation in this group of patients with no lymph node metastases included local recurrences within the thyroid bed, while the presence of lymph node metastases could be excluded histologically.

adenectomy (compartmentectomy), the number of lymph nodes surgically excised and the number of tumor-involved lymph nodes was evaluated by a quantitative histological analysis (Table 2). There were no significant differences in the number of surgically excised lymph nodes in the primary operations compared to recurrent surgical interventions. The number of tumor-involved lymph nodes was slightly less in recurrent operations compared to primary interventions. All primary operations that have been followed by reoperations with the compartmentectomy technique have been performed by the conventional (i.e., selective) lymphadenectomy technique or without any lymph node excision.

Postoperative Serum Calcitonin Concentrations

Postoperative serum calcitonin concentrations after pentagastrin stimulation were analyzed by comparing patients with different types of lymph node metastases (Table 3) and by comparing the effect of the two lymph node dissection techniques, i.e. selective versus systematic lymphadenectomy (Table 4). As shown in Table 3, the number of patients biochemically cured

Table 4. Normal postoperative pentagastrin-stimulated serum calcitonin concentrations after a selective versus systematic lymphadenectomy (n = 98) in 70 patients with sporadic and hereditary medullary thyroid carcinoma[a]

Lymph node status[b]	Selective lymphadenectomy		Systematic lymphadenectomy	
	First operation (%)	Recurrent operation (%)	First operation (%)	Recurrent operation (%)
NO	2/2 (100.0)	2/2 (100.0)	10/10 (100.0)	1/1 (100.0)
N1[c]	3/21 (14.3)	2/38 (5.3)	4/10 (40.0)	3/14 (21.4)
Total	5/23 (21.7)	4/40 (10.0)	14/20 (70.0)	4/15 (26.7)

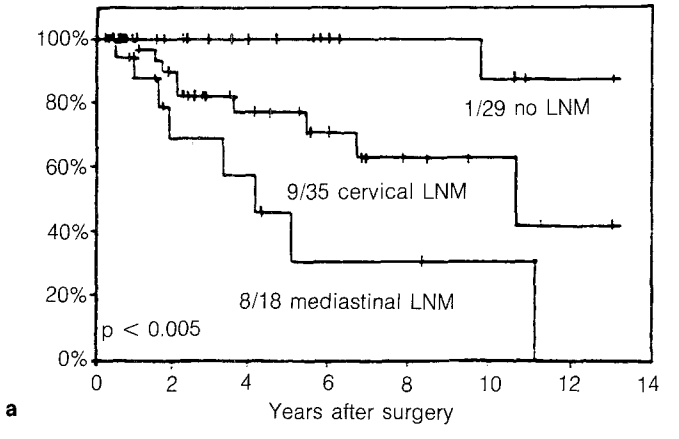
NO, no lymph node metastases; N1, regional lymph node metastases.
[a] In 12/82 patients no lymphadenectomy was performed.
[b] Lymph node status a definite histological analysis of the surgical specimen according to the UICC classification of TNM categories (24).
[c] The calculated P value for node-positive patients after selective versus systemtic lymphadenectomy was $P < 0.01$.

after a total thyroidectomy either with or without lymphadenectomy was significantly less in patients with lymph node metastases (11 of 53 patients, 20.8%) as compared to those without lymph node metastases (24 of 29 patients, 82.7%). Of the node-positive patients, 11 (26.8%) of 41 patients with Type C or Type A lymph node metastases were cured biochemically but no patients with bilateral lymph node metastases (Type B or D) were cured biochemically.

As shown in Table 4, all patients without any lymph node metastases, proven by a definite histological analysis of surgical specimens, had normal postoperative pentagastrin-stimulated calcitonin concentrations. In node-positive patients, the number of interventions followed by normal postoperative calcitonin concentrations was significantly higher after a systematic lymphadenectomy (7 of 24 patients, 29.2%) than after a selective lymphadenectomy (5 of 59 patients, 8.5%) ($P < 0.01$). Two of 12 patients with a transsternal approach to the cervicomediastinal lymph nodes and normal postoperative serum calcitonin concentrations (Type C, Table 3) underwent systematic lymphadenectomy.

Local-Regional Recurrence After Symptomatic Versus Systematic Lymphadenectomy

Twenty-three (59%) of 39 patients who did not undergo lymphadenectomy at the initial operation had 34 recurrent operations. Eleven (48%) of 23 patients who underwent selective lymphadenectomy at the initial operation had 19 recurrent operations, and 2 (10%) of



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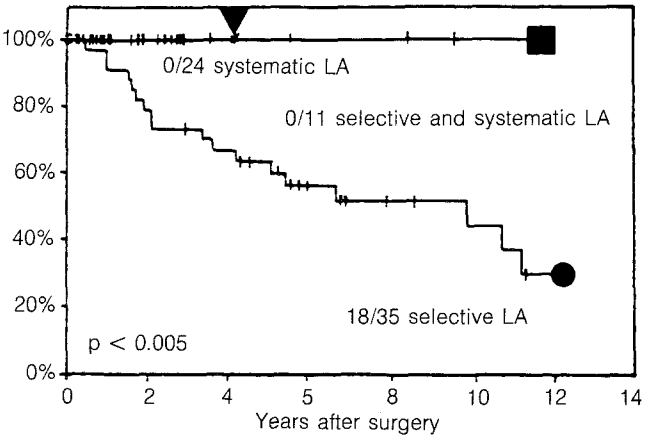

b

Fig. 6. a Survival curves for 82 MTC patients comparing patients without lymph node metastases (*LNM*) *vs* patients with cervical or with mediastinal LNM (defined as a result of the whole observation time of the individual patient) ($P < 0.005$ for each group). **b** Survival data for patients after a systematic lymphadenectomy (*LA*) with a maximum follow-up of 4.1 years (*solid triangle*), after selective (at first) and systematic LA (secondly) with a maximum follow-up of 12 years (*solid square*), and for patients after only a selective LA with a maximum follow-up of 12 years (*solid circle*). Only the patients undergoing an LA (n = 70) are included while those without LA (n = 12) are not. $P < 0.005$ refers to the patient groups after either a systematic LA or selective and systematic LA *vs* patients after a selective LA only

20 patients with an initial systematic lymphadenectomy had 2 recurrent operations due to the local-regional recurrence of MTC.

Patient Survival

There was no difference in the survival of patients with MTC with regard to sex. Due to an overrepresentation of the earlier tumor stages, hereditary MTC patients had a better prognosis compared to the patients with sporadic MTC ($P < 0.05$). Only 1 of 25 patients with hereditary MTC died due to progressive disease. In addition, there was a significant difference in survival for patients with pT1 (3 sporadic, 13 hereditary MTC), pT2 (28 sporadic, 11 hereditary MTC), pT3 (8 sporadic, 1 hereditary MTC), and pT4 tumors (18 sporadic, 0 hereditary MTC) ($P < 0.005$ for each group). MTC patients without lymph node metastases had a better prognosis than MTC patients with cervical or mediastinal lymph node metastases ($P < 0.005$ for each group) (Fig. 6A). The effect of systematic versus selective lymphadenectomy on the survival of MTC patients is shown in Fig. 6B. After systematic, or selective (first) and systematic lymphadenectomy (second), MTC patients had a better survival rate as compared to MTC patients after surgical treatment limited to selective lymphadenectomy ($P > 0.005$).

Surgical Complications

Complications after selective ($n = 63$) or systematic ($n = 35$) lymphadenectomy in the 82 patients are shown in Table 5. Non-tumor-related recurrent laryngeal nerve paralysis occured in only two patients with advanced pT4 tumors after recurrent selective lymphadenectomy during the first years of the study period. Paresis of the plexus brachialis (incomplete), n. phrenicus, and n. accessorius, respectively, was also observed in 4 patients.

Discussion

The development and manifestation of lymph node metastases represent the determining event in MTC. Patients with regional lymph node metastases have a reduced life expectancy and, in many cases, have to endure more than one reoperation with a considerably increased risk of surgical morbidity. Therefore, the implementation of an adequate surgical approach to MTC with regard to the extent of lymph node dissection as well as the appropriate surgical technique is critical in the overall prognosis of patients with MTC. This study has shown that increased radical surgery, including cervicomediastinal lymph node dissection, may improve the rates of recurrence and survival without any increased surgical morbidity if microdissection techniques are applied.

Soon after the establishment of MTC as a distinct clinicopathological entity of thyroid cancer, the importance of regional lymph node metastases was quickly recognized. In addition to total thyroidectomy, a systematic removal of lymph nodes in the vicinity of the thyroid, superior mediastinum, and lateral neck was initially recommended.[25] However, due to the frequent occurrence of regional micrometastases, both primary surgical treatment[6,8,11,16,19,26–29] and surgery of recurrent MTC has been associated with a relatively high rate of elevated postoperative serum calcitonin levels.[10,26,30] A normalization of pentagastrin-stimulated serum calcitonin levels after primary surgery of MTC has been reported in about 45% of MTC patients, whereas only 20% of patients showed normal serum calcitonin levels after re-exploration.

Persistent hypercalcitoninemia is a "common and vexing problem"[30] and we are seeing more and more such instances in centers concentrating on the diagnosis and treatment of MTC. The problem remains controversial regarding two major issues: (1) the definition of biochemical cure and adequate surgery (extent and

Table 5. Nerve pareses after a selective ($n = 63$) or systematic ($n = 35$) lymphadenectomy in 82 patients with medullary thyroid carcinoma

	First operation		Recurrent operation	
Nerve paresis[a]	Selective LA (%)	Systematic LA (%)	Selective LA (%)	Systematic LA (%)
Recurrent laryngeal	3/23[b] (17.4)	1/20[b] (5.0)	2/40 (5.0)	—
Brachial plexus	—	1/20[c] (5.0)	—	—
Phrenic	1/23 (4.3)	—	1/40 (2.5)	—
Accessory	—	—	—	1/15 (6.7)

LA, lymphadenectomy.
[a] All nerve pareses were unilateral.
[b] Resection of tumor infiltrated nerve(s).
[c] Incomplete paresis.

technique of regional lymphadenectomy) and (2) the treatment and survival of patients not cured biochemically but clinically free of disease. Biochemical cure after surgical treatment of MTC, i.e., a normalization of pentagastrin-and/or calcium-stimulated serum calcitonin levels, does not exclude the persistence of living tumor cells. It represents only the normalization of a biochemical tumor marker at the time of determination. False negative results, i.e., persistent tumor tissue in the presence of normal stimulated calcitonin levels, have been observed in about 5%–15% of MTC patients.[16,27] This is due to a subcritical but progressively increasing tumor cell mass after surgery and/or a decreasing cytological differentiation of tumor cells with decreasing calcitonin secretion,[31–33] a phenomenon recently described for differentiated thyroid carcinomas.[34,35] Thus, a biochemical cure does not imply a definite tumor-free status but may represent the actual tumor cell function and differentiation and depend on the observation period. Four of 82 patients in our series developed positive calcitonin tests 8, 17, 19, and 20 months after postoperative normalization of pentagastrin-stimulated calcitonin levels (all four patients have been included in the group of patients with pathological calcitonin stimulation tests at the time of follow-up). Three of these patients underwent repeat surgery and all had tumor cell-positive tissue probes, but there was a normalization of the calcitonin test after reoperation in only one patient. The fourth patient has not undergone repeat surgery.

In addition to the rate of false negative results, another unresolved problem in defining the biochemical cure in MTC is the method of testing. Apart from the calcitonin assay itself, which is measured by different antihuman calcitonin antisera,[19,30,36] most authors use only pentagastrin stimulation of calcitonin,[13,15,19,27,30,36] while others prefer routinely, or in the case of only slightly elevated calcitonin levels, the combined calcium-pentagastrin test.[10,11,16,17] For a further intercenter comparison of treatment results in MTC, the definition of biochemical cure after surgery should be standardized with regard to the calcitonin assay, stimulation procedures, and minimum postsurgical observation period.

As with the definition of biochemical cure, the definition of adequate surgery is far from standardized in a tumor stage-correlated approach in primary surgery of MTC. In contrast to preoperative parameters such as tumor palpation and calcitonin levels, new imaging procedures including ultrasonography, computed tomography, and magnetic resonace imaging as well as MIBG-, ^{99m}Tc (V) DMSA-, and ^{131}IF $(ab')_2$ anti carcinoembryonic antigen (CEA) scintigraphy[37] are able to give more exact information with regard to the extent and localization of the primary tumor and lymph node metastases. However, as long as specific prognostic markers in addition to these imaging methods are not available for routine use, the clinical tumor stage as defined by tumor size and lymph node status are the most important prognostic factors for intraoperative decision making. Our own present surgical strategy in MTC includes total thyroidectomy in all MTC patients because of the frequent intraglandular lymphangic spread of tumor cells[37] and the possibility of hereditary origin of MTC as shown postoperatively by histology and/or follow-up. In addition, lymph node dissection is undertaken in the central compartment between both vascular sheaths because of frequent micrometastases and the relativly high surgical-related morbidity of secondary surgery within the central area of the neck.

Whereas most surgeons agree with this strategy in respect to the central compartment, the technique of lymph node dissection and its extension to the lateral and mediastinal compartments is still debatable. Concerning the extent of lymph node dissection of lateral and mediastinal lymph node metastases, we did not find any direct correlation between the primary tumor size and the number and localization of regional lymph node metastases. It may be suspected from this clinical observation that MTC, as is already known from the variability of its histological appearance,[5] does not represent a homogenous tumor entity. Thus surgical decisionmaking with regard to lymph node dissection at present depends only on the macroscopic or microscopic identification of tumor-involved lymph nodes. This may be difficult due to the frequent occurrence of micrometastases that indeed cannot be excluded definitely either by macroscopy or by an excisional biopsy with frozen section. Therefore, a central and ipsilateral compartmentectomy (ipsilateral relative to the involved lymph nodes) seems to be justified in all cases in which central lymph node metastases are suspected by macroscopic or microscopic analysis of whole central compartmentectomy specimens. However, the effectiveness of this "plus 1-compartmentectomy" strategy still has to be substantiated by further studies.

On the basis of the results reported by Tisell et al.[10] and those shown in this study, the surgical technique of compartment-oriented microdissection of regional lymph node metastases seems to be significantly superior to selective lymphadenectomy not only with regard to the postoperative normalization of calcitonin levels and the reduced frequency of secondary surgical interventions due to persistant or recurrent MTC, but also based on the survival of patients. Although these results, in particular those of the patients' survival, have to be interpreted carefully due to the limited observation time, it must also be noted that there was

no particular selection for our patients who underwent a second procedure, neither for those with selective nor for those with a systematic, compartment-oriented approach to regional lymph node metastases. All patients with proven local recurrences or lymph node metastases underwent a second procedure after the first surgery regardless of the initial tumor stage or actual tumor extension. Moreover, although 60% of patients in the systematically operated group were hereditary cases while only 14% were so in the selectively operated group, the hereditary group also included "index"-cases with advanced tumors in both treatment groups. The statistical analysis of survival has also been carried out with regard to tumor stage and patients age, but the results gave no additional information to the data shown in Table 6D. This may be related to our patient material as it refers to other retrospective treatment studies dealing with such a rare tumor.

As revealed by our study, there is a group of MTC patients, consisting of at least 15%, who show cervicolateral or biparatracheal lymph node involvement in combination with mediastinal lymph node metastases inferior to the brachiocephalic vein, but without contralateral cervicolateral lymph node metastases. Therefore, in MTC patients with multiple suprajugular-paratracheal or supraclavicular lymph node metastases in addition to a cervical compartmentectomy, a transsternal mediastinal systematic lymph node dissection should be performed. If this observation can be substantiated by further studies, mediastinal lymph node metastases should no longer be considered as the last regional metastasizing area of MTC and may represent a frequent source of occult tumor persistence in asymptomatic hypercalcitoninemic patients.

However, secondary surgery for MTC still remains a difficult problem in those patients who, after adequate primary surgery, have persistent hypercalcitoninemia which cannot be localized even by invasive diagnostic procedures. Van Heerden et al.[30] recently clearly showed a remarkable 10-year survival rate for 86% of these patients. Thus, at present, we consider a conservative strategy to be justified, if these patients have undergone adequate neck surgery by the compartmentectomy technique including a transsternal mediastinal dissection for Type C and D MTC, and if an experienced clinical follow-up of the patients is carried out.

Acknowledgement. We are grateful to G. Martin for typing the manuscript and drawing the graphs.

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