Henry Ford Hospital Medical Journal

Volume 40 | Number 3 Article 28

9-1992

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Frequency and Significance of Cervicomediastinal Lymph Node Metastases in Medullary Thyroid Carcinoma: Results of a Compartment-Oriented Microdissection Method

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The frequency and significance of cervicomediastinal lymph node metastases have been investigated in 82 medullary thyroid carcinoma (MTC) patients retrospectively comparing two surgical techniques of lymph node dissection: selective lymphadenectomy (n = 63) versus compartment-oriented microdissection (n = 35). No positive correlation was observed between primary tumor size and the number of lymph node metastases. In patients with lymph node metastases proven histologically, 42% showed only cervical involvement (35% unilateral—type A, 7% bilateral—type B) and 22% cervicomediastinal lymph node involvement (15% cervico-unilateral and mediastinal—type C, 7% cervicobilateral and mediastinal—type D). Biochemical cure was 83% in node-negative patients but only 21% in node-positive patients. In node-positive MTC, calcitonin normalization was achieved in none with bilateral lymph node involvement but only in those unilateral lymph node metastases (31% in type A, 17% in type C). Survival and biochemical cure are significantly improved by application of the compartment-oriented microdissection method more so at primary surgery than at reoperation. (Henry Ford Hosp Med J 1992;40:264-7)

Lymph node metastases have been proven to be the most important prognostic factors in sporadic and hereditary medullary thyroid carcinoma (MTC) (1,2). A recent study demonstrated that the rate of node-positive patients was significantly lower in tumors smaller than 1 cm in diameter compared to larger tumors. However, in the entire group of MTC patients, no positive correlation was observed between primary tumor size and the occurrence and number of lymph node metastases (3). In hereditary MTC, central lymph node metastases have been observed even in patients with primary tumors not exceeding 5 mm in diameter (4).

In addition to the frequent and primary tumor size-independent occurrence of lymph node metastases, MTC tends to spread beyond the central area of the neck into the lateral and superior mediastinal lymph node compartments as well as to distant organs by developing multiple micrometastases. Important biological characteristics of MTC include not only its detectability by sensitive calcitonin (CT) studies (5-7) and imaging procedures (8) but also its tendency to metastasize early to cervicocentral nodes.

Due to the ineffectiveness of adjuvant treatment modalities (9,10), surgery is regarded as the treatment of choice in MTC. However, with growing recognition of the regional and distant micrometastatic process, standardization of surgical technique for lymph node dissection has been controversial as to the extent of lymph node removal which is indicated for different tumor sizes and/or macroscopic or microscopic involvement of regional lymph nodes (11-15). Along with the Goteborg group of Tisell et al (11), we developed a compartment-oriented microdissection (COMD) method of cervicomediastinal lymph node dissection aimed at the following: 1) the en block microdissection of anatomically defined compartments, and 2) quantitative analysis of the tumor involved and excised lymph nodes (3,4). In the present study we analyzed the frequency and location of regional lymph node metastases in sporadic and hereditary MTC, the biochemical cure after surgery relative to lymph node involvement, and the biochemical cure and survival after COMD versus selective lymphadenectomy (SLA).

Patients and Methods

This retrospective study concerns 82 MTC patients operated on initially or subsequently at the Medical School of Hannover's surgery department from 1970 to 1990 including 35 patients operated on by the COMD method since 1986. Twenty-five patients belonging to 11 families had the hereditary form of MTC (23 with multiple endocrine neoplasia type 2A [MEN 2A]

Submitted for publication: November 8, 1991.
Accepted for publication: January 27, 1992.
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Table 1
Primary Tumor Size and Types of Lymph Node Metastases in 82 MTC Patients*

Primary Tumor Size (cm)†	n	No Lymph Node Metastases (%)	Type A (%)	Type B (%)	Type C (%)	Type D (%)
< 1	10	7 (70)	2 (20)	0	1 (10)	0
1.0-1.9	15	9 (60)	5 (33)	0	0	1 (7)
2.0-3.9	32	11 (34)	13 (41)	3 (9)	4 (13)	1 (3)
> 4	25	2 (8)	9 (36)	3 (12)	7 (28)	4 (16)
Total	82	29 (35)	29 (35)	6 (7)	12 (15)	6 (7)

*Definition of lymph node involvement during the entire observation period of the patients. A four-compartmentectomy has been effected only in Type C and Type D MTC.
†Largest diameter.

Table 2
Biochemical Cure Rate Regarding Type of Lymph Node Metastases in 82 MTC Patients*

No Lymph Node Metastases†	Type A	Type B	Type C	Type D
24/29 (82.7%)	9/29 (31.0%)	0/6	2/12 (16.7%)	0/6

*Patients with normal stimulated calcitonin testing at the time of actual follow-up.
†A four-compartmentectomy has been effected only in Type C and Type D MTC.

and two with MEN 2B), and 57 had sporadic MTC. All patients received regular clinical follow-up until June 1991. Eighteen patients died due to metastasizing MTC, and two additional patients died as a result of other nontumor-related causes. The probability of survival was analyzed using estimated survival curves (16), employing the Mantel-Cox test and the generalized Wilcoxon test (17). Histological classification of MTC was performed according to the World Health Organization typing of thyroid tumors (18), and staging of primary tumors was done according to the Tumor-Node-Metastasis classification for malignant tumors of the UICC (19). Stimulated CT testing was performed by intravenous bolus injection of 0.5 μg pentagastrin/kg body weight and by obtaining peripheral blood levels at 0, 2, and 5 minutes after injection.

The compartment definition of cervicomediastinal lymph nodes and the definition of types of regional lymph node metastases in MTC is used as recently described (3,4). Compartment 1 represents the central cervical lymph node system right and left from the trachea between the trachea and carotid sheath and from the hyoid bone down to the brachiocephalic vein. Compartments 2 and 3 represent the right and left cervicolateral lymph node system between the carotid sheath and trapezoid muscle, from the subclavian vein up to the hypoglossal nerve, anterior, posterior, and between the fascicles of the cervical plexus. Compartment 4 represents the 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 upper mediastinum. The types of cervicomediastinal lymph node metastases in MTC have been defined as: 1) type A: MTC with unilateral lymph node metastases in the neck, confined to the perithyroidal, paratracheal, and/or cervicolateral lymph nodes; 2) type B: MTC with bilateral lymph nodes in the neck, including the contralateral side of the primary tumor; 3) type C: MTC with lymph node metastases on one side of the neck (including paratracheal lymph nodes on both sides) and within the upper mediastinum but without metastases contralateral to the cervicolateral compartment of the primary tumor; and 4) type D: MTC with lymph node metastases in all four cervicomediastinal compartments.

SLA, performed as the standard technique of lymph node dissection for MTC from 1970 to 1986, consists of the removal of lymph nodes or groups of lymph nodes with macroscopic tumor involvement. In contrast, the COMD method is achieved by the en bloc removal of anatomically defined compartments of lymph nodes, adipose tissue, and connective tissue with the aid of magnification. 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 lymph nodes involved by the tumor are documented quantitatively by histological analysis.

Results

The primary tumor size and the types of lymph node metastases in 82 MTC patients are shown in Table 1. As tumor size increased, the number of MTC patients without regional lymph node metastases decreased. Eighteen patients underwent a transsternal dissection of the superior mediastinal lymph node compartment. Although type C and type D lymph node involvement were predominantly observed in locally metastatic primary tumors with diameters exceeding 4 cm in diameter (11 [44%] of 25 patients), these types of lymph node involvement were documented also in 6 (13%) of 47 patients with T2 tumors. Type C lymph node metastases (i.e., cervico-unilateral and mediastinal lymph node involvement) could be shown in a total of 12 (15%) of 82 MTC patients (11 with sporadic MTC and 1 with hereditary MTC). Type D lymph node metastases (cervicobilateral and mediastinal lymph node involvement) were found in 1 (4%) of 25 hereditary and in 5 (9%) of 57 sporadic MTC patients.

The results of lymph node surgery relative to pentagastrin-stimulated CT levels are shown in Table 2. The data include the whole series of MTC patients having SLA or the COMD method. A total of 83% of node-negative MTC patients, compared to 21% of node-positive patients, had negative pentagastrin stimulation tests. In the case of synchronous or metachronous lymph node metastases, CT normalization was achieved in only 13% of patients if more than one operation was necessary compared to 33% of patients after adequate first surgery. Even after extensive cervical or cervicomediastinal compartmentectomy in type B and type D MTC, normalization of CT levels was not attained.

Biochemical results with the two types of surgical technique of lymph node dissection (SLA versus COMD) are given in Ta-

Table 3
Biochemical Cure After Selective Lymphadenectomy Versus Compartment-Oriented Microdissection in 70 Patients with Node-Positive MTC*

	SLA		COMD	
Lymph Node Status†	First Operation (%)	Reoperation (%)	First Operation (%)	Reoperation (%)
N0	2/2 (100)	2/2 (100)	10/10 (100)	1/1 (100)
N1	3/21 (14)	2/38 (5)	4/10 (40)	3/14 (21)
Total	5/23 (22)	4/40 (10)	14/20 (70)	4/15 (27)

*Patients with normal stimulated calcitonin testing at the time of follow-up. Twelve of the entire group of 82 MTC patients had no lymph node surgery.
†According to the UICC classification of 1987.
SLA = selective lymphadenectomy (n = 63); COMD = compartment-oriented microdissection (n = 35).

Table 4
Present Surgical Strategy to MTC

Indications	Type of LNM*	Extent of Surgery†
All MTC		TT, C1
Cervicounilateral LNM	A	TT, C1 + C2/3
Cervicobilateral LNM	B	TT, C1-C3
Cervicounilateral and mediastinal LNM	C	TT, C1-C4
Cervicobilateral and mediastinal LNM	D	TT, C1-C4

*LNM = lymph node metastases (for definition of types see Patients and Methods section).
†TT = total thyroidectomy (for C1, 2, 3, 4 definition of compartments see Patients and Methods section).

ble 3. In node-positive MTC, normalization of pentagastrin-stimulated serum CT levels increased from 14% to 40% after first surgery and from 5% to 21% after reoperative surgery if the COMD method was performed.

Survival data for our MTC patients revealed a significantly better prognosis for patients without lymph node metastases compared to those with lymph node metastases (Figure, left panel). Within node-positive groups, those with mediastinal lymph node metastases had the most unfavorable prognosis. The survival data of node-positive MTC patients were significantly improved by the COMD technique as compared to the results obtained after SLA (Figure, right panel).

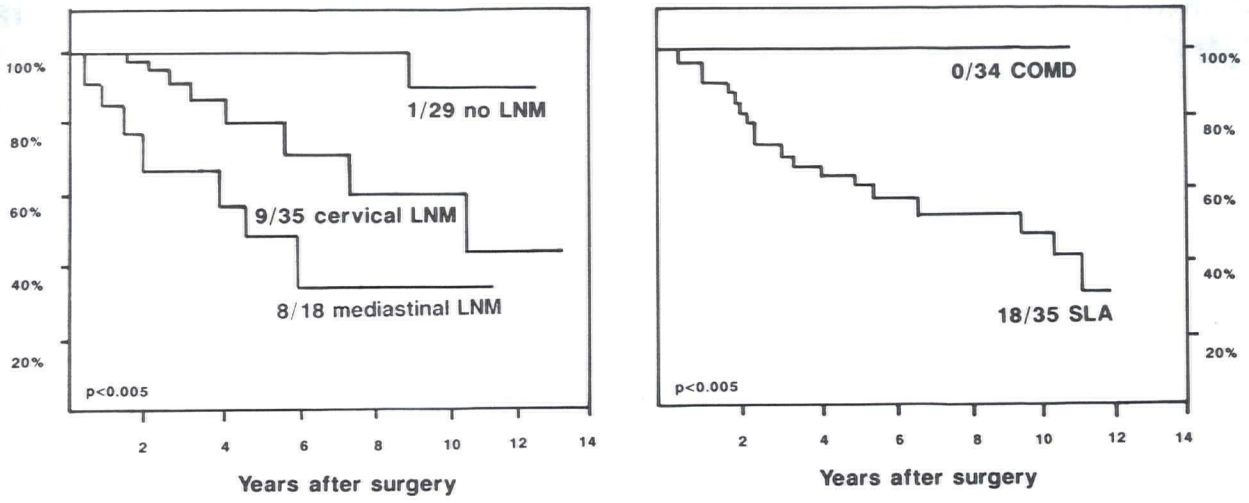
Discussion

This study confirms earlier studies demonstrating the significance of lymph node metastases as a dominating prognostic factor in MTC (1). In addition, this and other reports have shown that more radical surgery regarding cervicomediastinal lymph node dissection using microdissection techniques may improve the recurrence rate and increase survival without increasing surgically related morbidity (3,4,11).

The COMD technique was originally described by Tisell et al in 1986 (11). At that time our own technique of lymph node dissection changed to more extensive procedures due to disappointing results of SLA in node-positive MTC. Because of the observed micrometastatic lymphangitic spread of MTC, we developed a compartment-oriented approach to node-positive MTC defined by the types of lymph node metastases found in patients with cervicomediastinal lymph node metastases (Table 4). With this strategy, all patients with MTC, regardless of the presence or absence of lymph node metastases, undergo a total thyroidectomy and microdissection of the cervicocentral compartment. In the case of macroscopic or microscopic evidence of lymph node metastases, unilateral (if lymph node metastases are confined to one side of the neck) or bilateral (with lymph node involvement on both sides of the tracheal axis) microdissection of the cervicolateral compartment is added.

By meticulous analysis of three- and four-compartmentectomy tissue specimens, it has been proven that superior mediastinal lymph node involvement occurs not only in patients with bilateral cervicolateral lymph node metastases but also in some patients with unilateral cervical lymph node metastases. This type (type C) of lymphangic spread has been observed in 19% of sporadic and 4% of hereditary MTC in our series of 82 MTC patients. In two of 12 patients with type C lymph node metastases, a normalization of CT levels resulted after the four-compartmentectomy procedure, corresponding to the results achieved in patients with cervico-unilateral (type A) and cervicobilateral lymph node metastases of MTC (type B) (Table 2). Nine (31%) of 29 patients with type A lymph node metastases have been observed to be biochemically cured, although this has not happened with any of the six cases of type B. Since all of the patients with type B lymph node metastases had only a cervical lymph node dissection, it is suspected that at least some had microscopic foci within the superior mediastinum or elsewhere.

Due to the current detection limits of imaging methods (8) as well as venous catheterization procedures (20), the frequency and significance of superior mediastinal lymph node metastases and the exact indications for transsternal mediastinectomy remain to be investigated by further interdisciplinary surgical, pathological, and localization studies so that further improvement in treatment results will be attained.



Figure—Prognostic significance of lymph node status and technique of lymphadenectomy in 82 MTC patients (LNM = lymph node metastases, COMD = compartment-oriented microdissection, SLA = selective lymphadenectomy).

Acknowledgment

This work was supported by Tumorzentrum Hannover.

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