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Patterns of Nodal Metastases in Palpable Medullary Thyroid Carcinoma

Recommendations for Extent of Node Dissection

Jeffrey F. Moley, MD, and Mary K. DeBenedetti, RN, BSN

From the Department of Surgery, Washington University School of Medicine, St. Louis, Missouri, and John Cochran Veterans Administration Medical Center, St. Louis, Missouri

Objective
To establish the frequency, pattern and location of cervical lymph node metastases from palpable medullary thyroid carcinoma (MTC). Recommendations are made regarding the extent of surgery for this tumor.

Summary Background Data
Medullary thyroid carcinoma is a tumor of neuroendocrine origin that does not concentrate iodine. Surgical extirpation of the thyroid tumor and cervical node metastases is the only potentially curative therapeutic option. Patterns of node metastases in the neck and guidelines for the extent of dissection for palpable MTC are not well established.

Methods
Seventy-three patients underwent thyroidectomy for palpable MTC with immediate or delayed central and bilateral functional neck dissections. The number and location of lymph node metastases in the central (levels VI and VII) and bilateral (levels II to V) nodal groups were noted and were correlated with the size and location of the primary thyroid tumor. Intraoperative assessment of nodal status by palpation and inspection by the surgeon was correlated with results of histologic examination.

Results
Patients with unilateral intrathyroid tumors had lymph node metastases in 81% of central node dissections, 81% of ipsilateral functional (levels II to V) dissections, and 44% of contralateral functional (levels II to V) dissections. In patients with bilateral intrathyroid tumors, nodal metastases were present in 78% of central node dissections, 71% of functional (levels II to V) node dissections ipsilateral to the largest intrathyroid tumor, and 49% of functional (levels II to V) node dissections contralateral to the largest thyroid tumor. The sensitivity of the surgeon's intraoperative assessment for nodal metastases was 64%, and the specificity was 71%.

Conclusion
In this series, >75% of patients with palpable MTC had associated nodal metastases, which often were not apparent to the surgeon. Routine central and bilateral functional neck dissections should be considered in all patients with palpable MTC.

Medullary thyroid carcinomas (MTC) are neuroendocrine cancers that arise from the thyroid C cells. They occur in sporadic and hereditary (multiple endocrine neoplasia type 2 and related syndromes) clinical settings. These tumors secrete the tumor marker calcitonin, which is extremely useful in the screening of individuals predisposed to the hereditary forms of the disease, and in the follow-up of patients who have been treated. Young patients with occult MTC detected by genetic screening of families with hereditary MTC have a low frequency of node metastases and may be cured by thyroidectomy and central node clearance.[1] Most cases of sporadic MTC and cases of hereditary MTC not detected by genetic or biochemical screening, however, present as a palpable neck mass. Cervical lymph node metastases in these patients have been reported to occur in 25% to 63% of patients, depending on the series.[2–6] Metastases occur in the central compartment—perithyroidal, paratracheal (level VI nodes), and upper mediastinal nodes (level VII nodes) (Fig. 1). The central compartment includes

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Correspondence: Jeffrey F. Moley, MD, Department of Surgery, Washington University School of Medicine, 5108 Queeny Tower, One Barnes Hospital Plaza, St. Louis, MO 63110.
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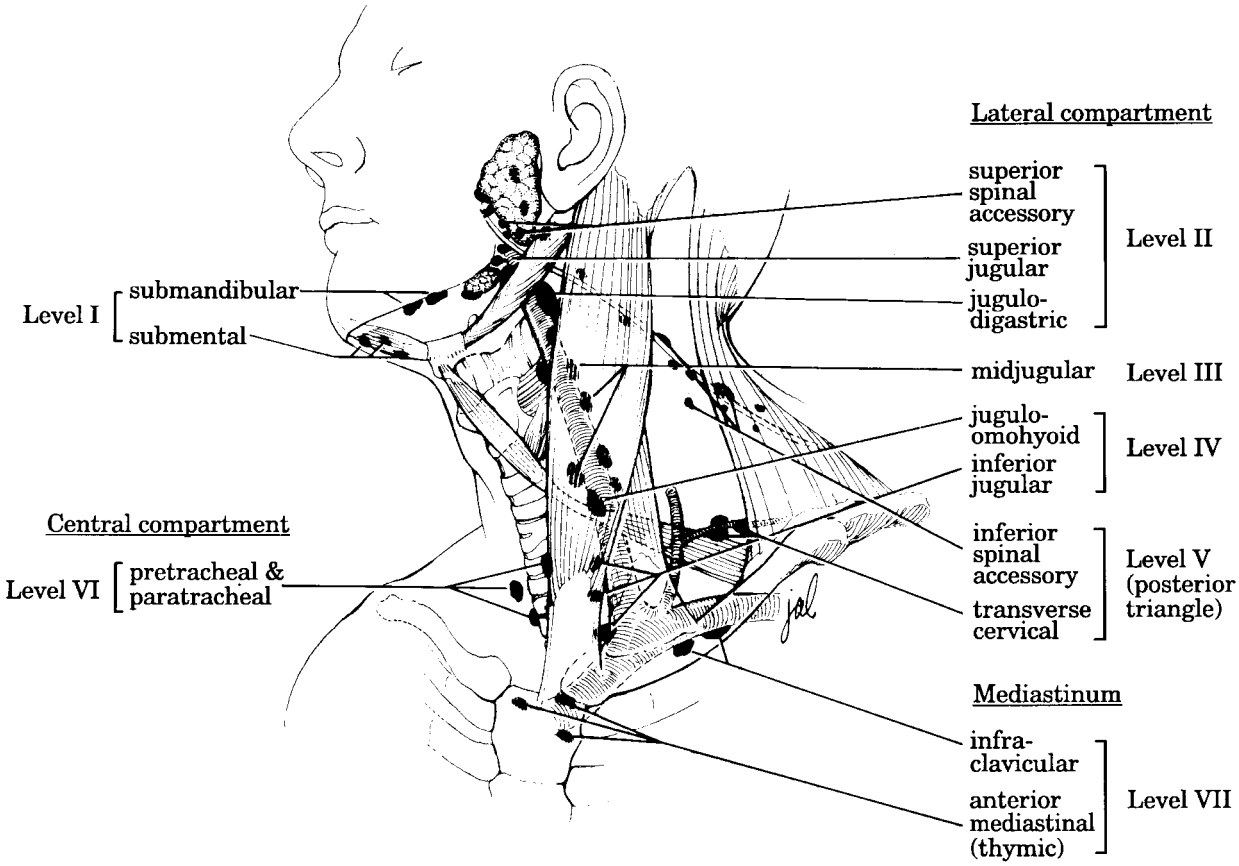

Figure 1. Anatomic landmarks and lymph node compartments in the neck and upper mediastinum encountered in surgical reinterventions for MTC. Central compartment is delimited inferiorly by the innominate vein, superiorly by the hyoid bone, laterally by the carotid sheaths, and dorsally by the prevertebral fascia. It comprises lymphatic and soft tissues around the esophagus, and pretracheal and paratracheal lymph nodes that drain the thyroid bed (level VI). The submandibular nodal group (level I) is subsumed in the central compartment in some classifications. Lateral compartments span the area between the carotid sheath, the sternocleidomastoid muscle, and the trapezius muscle. The inferior border is defined by the subclavian vein, and the hypoglossal nerve determines the superior boundary. The lymph node chain adjacent to the jugular vein is divided cranially to caudally in superior jugular nodes (level II), midjugular nodes (level III), and inferior jugular nodes (level IV). Lymph nodes in the posterior triangle between the dorsolateral sternocleidomastoid muscle, the trapezius muscle, and the subclavian vein are classified as level V nodes. Mediastinal lymphatic tissue is referred to as level VII lymph nodes. (From Musholt TJ, Moley JF. Management of recurrent medullary thyroid carcinoma after total thyroidectomy. Prob Gen Surg 1997; 14:89–110, with permission)

tissue on the trachea, extending to the carotid sheath, and from the hyoid bone to the innominate vein. Within this compartment, spread is commonly bilateral. Lymphatic spread occurs to the lateral neck compartment. Middle and lower jugular nodes (levels III and IV) are frequently involved. High jugular (level II) and posterior triangle (level V) nodes are involved less frequently.[7–9]

Adequate surgical extirpation is the only curative form of therapy for MTC at present. Unlike differentiated thyroid cancers, MTC cells do not take up iodine, and iodine-131 treatment is ineffective.[10] External beam radiation therapy and cytotoxic chemotherapy have not been found to be effective consistently.[11–13] The recommended surgical procedure for palpable MTC has not been well established. In the recently distributed *Practice Guidelines for Major Cancer Sites*, developed by the Society of Surgical Oncology, total thyroidectomy was recommended, but node dissections were recommended only for clinically palpable nodes.[14] This may be an effective strategy for differentiated thyroid cancer, where suppression with thyroxine and radioactive iodine ablation are extremely effective adjuncts to surgery, but MTC cells do not respond to these nonsurgical treatments. In a recent series of reoperations for recurrent or residual MTC, the authors judged that >80% of referred patients had an inadequate primary operation.[15] Overall, persistent disease, evidenced by elevated calcitonin levels, is present in >50% of patients after surgery for MTC.[16,17] In the absence of effective adjuvant therapy, there is a need

to define or predict the extent of spread of these tumors at the time of diagnosis so that appropriate surgical resection can be performed.

In the present report, we analyzed the distribution of nodal metastases in a series of patients in whom MTC presented as a palpable neck mass; central and bilateral cervical nodes were removed and examined histologically. We found that the incidence of central (levels VI and VII) node involvement was extremely high, regardless of the size of the primary tumor. There was also frequent involvement of ipsilateral and contralateral (levels II, III, and IV) nodes. This supports our recommendation that these nodes be removed routinely in patients with palpable primary MTC.

MATERIALS AND METHODS

Patients

Between 1993 and 1998, we evaluated 162 patients with primary, residual, or recurrent MTC who initially had a palpable mass. Forty-seven patients did not undergo cervical node dissection because of distant metastases or medical conditions that mitigated against further surgery. Twelve patients with recurrent or residual MTC without apparent distant metastases chose not to have any further surgery after initial thyroidectomy at an outside hospital. Ninety patients underwent total thyroidectomy plus lymph node dissection. The timing of total thyroidectomy and node dissection was as follows: 36 patients had thyroidectomy and node dissections within 1 year of diagnosis, 7 patients had node dissections within 2 years of thyroidectomy, and 47 patients had node dissections 3 or more years after thyroidectomy. Of these 90 patients, 69 had total thyroidectomy and central and bilateral functional node dissections and are included in this analysis (Figs. 2 and 3). The remaining 21 patients had total thyroidectomy and central and unilateral functional neck dissections. Thirteen of these patients had palliative resections based on presence of distant metastatic disease or extensive invasion of local structures; they were not included in this analysis. Of the remaining eight patients, all of whom underwent surgery with curative intent, four have normal stimulated calcitonin levels and therefore are assumed to have no tumor in the undissected side of the neck. They are included in this analysis. The other four patients, with persistently elevated calcitonin levels, do not have nodal tissue from both sides of the neck for evaluation and therefore are not included in this analysis. There are, therefore, 73 patients in whom pathologic examination of the thyroid and central (levels VI and VII) and bilateral cervical nodes (levels II to V) was done; they form the basis of this report.

Cervical and Upper Mediastinal Nodes

Figure 1 shows the nodal groups of the neck. The nodes available for analysis in this study came from therapeutic neck dissections for metastatic MTC. In the central node dissections, all residual thyroid tissue and nodal tissue within the central compartment was removed (levels VI and VII nodes). This was carried out from the level of the hyoid bone, along the larynx, and along the recurrent nerves to a level below the innominate artery on the right side, and to a comparable level behind the clavicle on the left side. All tissue on the anterior surface of the trachea, including any

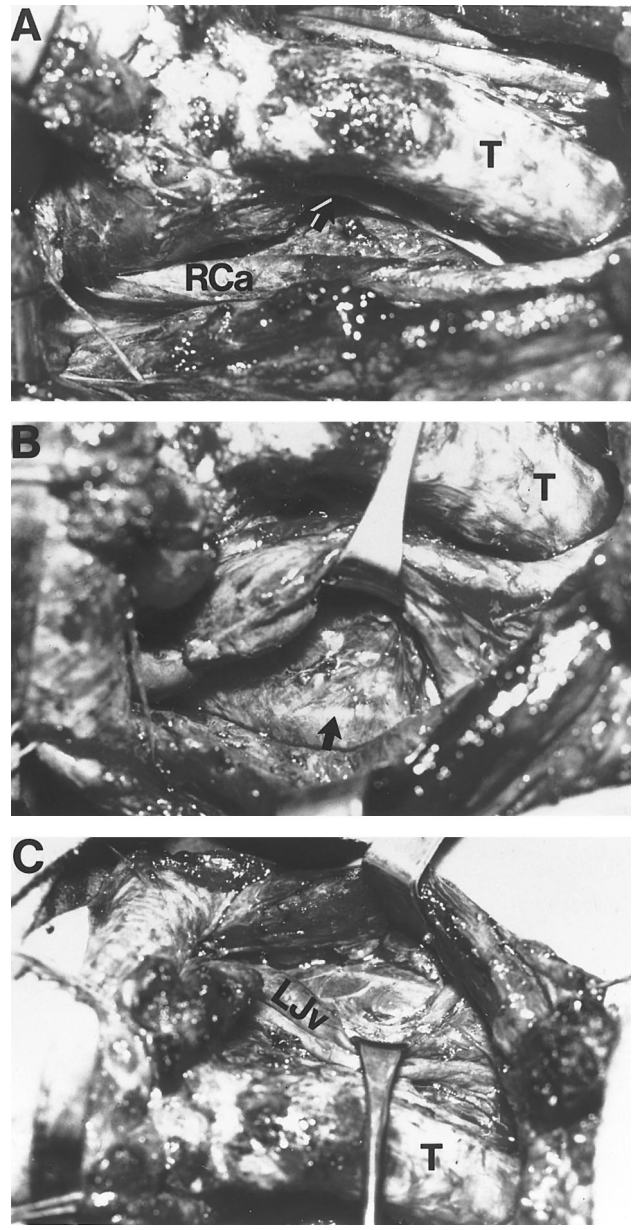

Figure 2. Views of the neck after total thyroidectomy, parathyroidectomy, central (levels VI, VII) node dissection, and bilateral (levels II to IV) node dissections. The patient's head is to the left and the neck contents are viewed from the right side. (A) Thyroid and central nodes have been removed. T, trachea; RCa, right carotid artery. Arrow demonstrates the right recurrent laryngeal nerve. (B) Right carotid artery and jugular vein are retracted medially. Levels III and IV nodes have been removed, and the phrenic nerve (arrow) is visible on the anterior scalene muscle. (C) Same dissection as (B), on left. LJv, left jugular vein.

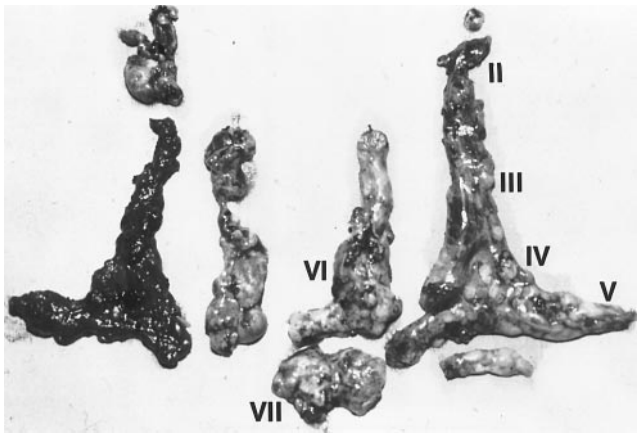

Figure 3. Resected lymph nodes from a patient with multiple endocrine neoplasia type 2B. Metastatic deposits were found in level VI nodes. II, III, IV, V, VI, VII- lymph node levels in resected specimens. Level II: high jugular nodes. Level III: middle jugular nodes. Level IV: low jugular nodes. Level V: posterior triangle nodes (partial resection). Level IV: paratracheal nodes. Level VII: superior mediastinal nodes. (From Moley JF. Medullary thyroid cancer. In: Clark O, Duh Q-Y, eds. Textbook of endocrine surgery. Philadelphia: WB Saunders; 1997, with permission.)

visible thymic tissue, was removed (Fig. 2). The lateral boundaries of this part of the dissection were the carotid sheaths. These procedures were carried out using a low collar incision, with extension upward laterally along the posterior third of the sternocleidomastoid muscle. Median sternotomy was used in two patients.

Lateral Nodes

Nodes lateral to the central compartment were removed in a functional neck dissection. In this procedure, mobilization of the carotid sheath and removal of all nodal tissue anterior to the carotid sheath up to the level of the facial vein was done. The posterior jugular chain of nodes (lower level II, level III, and level IV) was dissected off the posterior cervical fascia and excised. Nodes anterior to the carotid sheath, including jugulodigastric (level II) nodes, were removed. The lateral boundary of this dissection was the cervical plexus at the posterior border of the sternocleidomastoid muscle. Posterior triangle nodes (level V) were sampled, and in four patients a formal level V node dissection was done, stripping nodes off the brachial plexus, subclavian vessels, and spinal accessory nerve.

Pathologic Examination

Pathologic materials from any previous surgical procedure for MTC were reviewed by the Department of Pathology, Washington University School of Medicine, St. Louis. Tissues removed were fixed in formalin, stained with hematoxylin and eosin, and examined by members of the same department. Nodes classified as central included levels VI and VII, perithyroidal, and upper mediastinal and thymic nodes reached through the neck. No attempt was made to categorize central nodes as right or left. This entire compartment was removed *en bloc*. Lateral nodes were classified as right or left levels II, III, IV, and/or V nodes. Jugulodigastric nodes were considered to be level II nodes. The size and location of the primary tumor and its multicentricity were assessed from pathology reports.

Intraoperative Assessment of Nodes

Operative notes were reviewed and correlated with pathology reports to determine how often metastatic nodal involvement was apparent to the surgeon by inspection or palpation. Two hundred twenty-four nodal groups were assessed by a surgeon (JFM) during surgery, and his assessment was compared with the results of the histologic examination.

Statistics

Data on tumor size are presented as mean ± SEM. Groups were compared by analysis of variance.

Calcitonin Testing

After an intravenous infusion of calcium gluconate (2 mg/kg over 1 minute) followed by pentagastrin (0.5 μg/kg over 5 seconds), blood samples were obtained before and at 1, 2, 3, and 5 minutes after the infusion. In this report, calcitonin levels reported are peak stimulated values.

RESULTS

Patients and Primary Thyroid Tumor Size

Characteristics of the 73 patients are summarized in Table 1. In 32 patients, the intrathyroid MTC was confined to

Table 1. CHARACTERISTICS OF PATIENTS WITH MTC WHO HAD TOTAL THYROIDECTOMY AND CENTRAL AND BILATERAL CERVICAL NODE DISSECTIONS

Number of patients	73
Sporadic MTC	35
Multiple endocrine neoplasia type 2A	27
Multiple endocrine neoplasia type 2B	11
Female	45
Male	28
Age: 0–25	25
25–45	35
46–65	12
65+	1

MTC, medullary thyroid carcinoma.

Table 2. NUMBER OF LYMPH NODES RESECTED FROM CENTRAL AND LATERAL COMPARTMENTS IN PATIENTS WITH UNILATERAL AND BILATERAL MTC

Unilateral Intrathyroid MTC (32 patients)			
	Mean ± SEM	**Range**	**Median**
Central nodes total	12 ± 1.6	2–29	10
Central nodes with metastases	4.4 ± 0.9	0–23	3
Ipsilateral (II–V) total	24 ± 2.2	9–49	22
Ipsilateral (II–V) with metastases	6.3 ± 1.5	0–36	3.5
Contralateral (II–V) total	11.7 ± 1.6	1–29	12
Contralateral (II–V) with metastases	1 ± 0.4*	0–8	0
Bilateral Intrathyroid MTC (41 Patients)			
	Mean ± SEM	**Range**	**Median**
Central nodes total	14.8 ± 1.6	2–34	14
Central nodes with metastases	4.6 ± 0.8	0–21	3
Ipsilateral (II–V) total	17.5 ± 2.4	2–61	13
Ipsilateral (II–V) with metastases	2.5 ± 0.5	0–9	2
Contralateral (II–V) total	22.2 ± 3.2	2–85	19.5
Contralateral (II–V) with metastases	5.3 ± 1.9	0–45	1.0

In patients with bilateral tumors, ipsilateral and contralateral refer to the relation of nodes to the side of the largest primary tumor.
* $p < 0.001$ *vs.* central and ipsilateral (II–V) positive nodes in patients with unilateral intrathyroid tumors, and *vs.* contralateral (II–V) positive nodes in bilateral intrathyroid tumors.
MTC, medullary thyroid carcinoma.

one lobe of the gland. These cases are designated "unilateral intrathyroid tumors." Forty-one patients had intrathyroid tumors in both thyroid lobes; these are designated "bilateral intrathyroid tumors." In patients with unilateral intrathyroidal MTC, 24 of the primary tumors were on the left and 8 were on the right. The average tumor diameter was 2.7 ± 0.3 cm (range 0.7 to 6 cm, median 2.0 cm).

Lymph Node Involvement

The lymph nodes identified in resected specimens (total number and number with metastases) are summarized in Table 2. The number of positive central nodes was similar for patients with unilateral and bilateral intrathyroid tumors. In patients with unilateral thyroid tumors, the number of positive contralateral (levels II to V) nodes was less than the number of positive nodes observed in the central (levels VI and VII) and ipsilateral (levels II to V) compartments ($p < 0.001$). It was also less than the number of positive nodes contralateral to the largest intrathyroid tumor in patients with bilateral intrathyroid tumors ($p < 0.001$).

Tables 3 and 4 show the distribution and frequency of nodal metastases in patients with unilateral intrathyroid MTC and bilateral intrathyroid MTC. The presence of positive nodes in central, ipsilateral, and contralateral (levels II to V) nodal groups was correlated with the size of the intrathyroid primary tumor. The frequency of node metastases in patients with unilateral intrathyroid tumors was extremely high: 81% of these patients had positive nodes detected in the central and right and left (levels VI and VII) nodes and ipsilateral (levels II to V) compartments, and 44% had positive nodes detected in the contralateral (levels II to V) nodal groups. This pattern was present even in patients with unilateral intrathyroid tumors <2 cm: 11 of the 13 such patients had central nodal metastases, 11 of the 13 had ipsilateral (levels II to V) metastases, and 4 of the 13 had contralateral (levels II to V) metastases.

This pattern was again seen in patients with bilateral intrathyroid tumors. Seventy-eight percent of these patients had metastatic involvement of central nodes and (levels II to V) nodes ipsilateral to the largest primary tumor, and 44% had metastatic involvement of contralateral (levels II to V) nodes. The pattern was again seen in patients whose largest primary tumor was <2 cm: 13 of the 19 such patients had metastases to central nodes, 15 of the 19 had metastases to

Table 3. UNILATERAL INTRATHYROID TUMORS: FREQUENCY AND DISTRIBUTION OF NODAL METASTASES

Tumor Size (cm)	No. of Patients	Patients with Central Node Metastases	Patients with Ipsilateral Levels II–V Metastases	Patients with Contralateral Levels II–V Metastases
0–0.9	4	3/4	3/4	1/4
1–1.9	9	8/9	8/9	3/9
2–2.9	5	4/5	3/5	3/5
3–3.9	5	2/5	4/5	3/5
≥4	9	9/9	8/9	4/9
Total	32	26/32 (81%)	26/32 (81%)	14/32 (44%)

Central nodes refer to right and left levels VI and VII nodes.

Table 4. BILATERAL INTRATHYROID TUMORS: FREQUENCY AND DISTRIBUTION OF NODAL METASTASES

Size of Largest Tumor (cm)	No. of Patients	Patients with Central Node Metastases	Patients with Ipsilateral Levels II–V Metastases	Patients with Contralateral Levels II–V Metastases
0–0.9	12	8/12	9/12	4/12
1–1.9	7	5/7	6/7	4/7
2–2.9	8	7/8	4/8	5/8
3–3.9	7	7/7	6/7	5/7
4 or larger	7	5/7	4/7	2/7
Total	41	32/41 (78%)	29/41 (71%)	20/41 (49%)

Central nodes refer to right and left levels VI and VII nodes.

ipsilateral (levels II to V) nodes, and 8 of the 19 had metastases to contralateral (levels II to V) nodes.

Accuracy of Intraoperative Assessment

Operative notes included the surgeon's assessment of nodal status by palpation and inspection for 224 nodal groups in 73 patients. Nodal groups were categorized as central, right lateral (levels II to V), and left lateral (levels II to V). In 64 nodal groups, the surgeon's assessment indicated that the nodes contained one or more metastatic deposits, and the histologic examination showed metastatic tumor (true-positive results) (Fig. 4). In 36 nodal groups, the surgeon's assessment indicated that the nodes were positive, but histologic examination indicated no metastatic involvement (false-positive results). In 88 nodal groups, the surgeon's assessment indicated that the nodes did not contain metastatic deposits, and histologic examination verified this (true-negative results). In 36 nodal groups, the surgeon's assessment indicated that the nodes did not contain any metastatic deposits, but histologic examination showed metastases (false-negative results). The sensitivity of intraoperative assessment by the surgeon in this series was 64%, and the specificity was 71%.

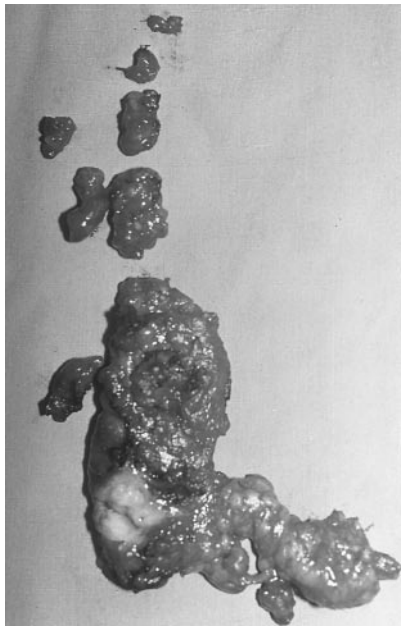

Figure 4. Left levels III and IV nodes from a patient with sporadic MTC. A large metastatic deposit can be seen in the lower portion of the nodal group.

Calcitonin Levels

Calcitonin levels were measured in all patients before and after surgery using the protocol of calcium and pentagastrin stimulation described above. Stimulated calcitonin levels were reduced to normal in 24 of 73 patients (33%) after these surgical procedures. Levels were decreased by 50% or greater in all patients except eight.

DISCUSSION

Medullary thyroid carcinoma is a slow-growing but often lethal cancer. Nodal involvement is a significant predictor of death. In a series of 160 patients treated at the Mayo Clinic, 20-year mortality rates were 24% for node-positive patients and 3.5% for node-negative patients.[18] Surgical extirpation offers the only chance of cure. Nonsurgical therapies, including radioactive iodine, external beam radiation therapy, and chemotherapy, have not been shown to be effective against this tumor.[10–12] In patients with persistent or recurrent disease, as evidenced by elevated calcitonin levels, reoperation with removal of nodal metastatic disease is the only therapeutic intervention shown to reduce calcitonin levels reliably and reproducibly in a significant number of patients.[8,15,17,19–21] Normalization of calcitonin levels after extensive node dissection by an experienced surgeon has been reported in approximately 33% of patients. Reoperations, however, are associated with a small but significant risk of complications, including hypoparathyroidism, recurrent nerve injury, and thoracic duct leak. It would be in the patient's best interest to perform an adequate dissection at

the initial procedure. This is particularly true of central node dissections, which are done most safely at the time of thyroidectomy. If done as a reoperation after thyroidectomy, identification of recurrent nerves and parathyroid glands can be extremely difficult. Performance of an adequate initial operation depends on the surgeon's knowledge of the diagnosis and the predicted pattern of nodal spread of the thyroid tumor. This knowledge will allow the surgeon to remove all occult metastatic disease in the neck at the initial procedure.

Patients with occult MTC detected by genetic screening of families with multiple endocrine neoplasia type 2 have a low frequency of node metastases and may be adequately treated by thyroidectomy and central node clearance.[1] Guidelines recommending the extent of node dissection for palpable MTC have not been well established.[14]

Previous well-defined estimates of nodal involvement in MTC have ranged from 25% to 63%.[2–6] In these series, however, central (levels VI and VII) and bilateral (levels II to V) node dissections were not routinely performed, and therefore the true incidence of nodal involvement in MTC has not been established. In the present series, central and right and left lateral nodes were evaluated in 73 patients, and there was an alarmingly high incidence of nodal involvement. Overall, central nodes were involved with metastases in 58/73 (79%). Even contralateral (levels II to V) nodes were frequently involved. In patients with bilateral intrathyroid MTC, levels II to V nodes contralateral to the largest intrathyroid tumor were involved in 20/41 cases (49%). In patients with unilateral thyroid tumors, the absolute number of positive nodes in contralateral (levels II to V) nodes was lower than in ipsilateral nodes; however, the frequency with which at least one positive node was found in the contralateral (levels II to V) nodal group was still high (14/32 [44%]).

Intraoperative palpation of nodes was not an accurate predictor of the presence or absence of metastases. The sensitivity of the intraoperative assessment by an experienced surgeon was only 64%, and the specificity was 71%. Therefore, reliance on intraoperative assessment would miss involved nodes 36% of the time. The strategy of resecting only "clinically involved" nodes is effective in differentiated thyroid cancer, where extremely effective adjuvant therapy is available. However, there are no effective adjuvant treatments for MTC, although the clinical course of MTC is often indolent, and 15-year survival rates of 50% to 85% have been reported with no further treatment.[17,18,22]

It may be argued that the institutional bias in this series is toward patients with nodal disease because many patients with elevated calcitonin levels were referred after primary surgery for palpable MTC. Of the 90 patients who underwent surgery at our institution, 54 had reoperations 2 or more years after a primary procedure. Patients with palpable MTC who have normal postoperative calcitonin levels are not frequently seen at our institution, and the frequency of that outcome is difficult to establish. Other series, however, have reported that >50% of patients who undergo surgery for MTC have persistently elevated calcitonin levels after surgery.[16,22,23] These series include patients with nonpalpable tumors detected by biochemical screening of kindreds with hereditary forms of MTC. The rates of persistent hypercalcitoninemia in patients with palpable disease can be assumed to be higher.

Based on these results, our recommendation for patients with palpable MTC is total thyroidectomy, parathyroidectomy with autotransplantation, central neck dissection (right and left levels VI and VII), and bilateral functional (levels II to V) neck dissections, as described above. We recommend that these patients have a four-gland parathyroidectomy with autotransplantation to either the sternocleidomastoid muscle (patients with multiple endocrine neoplasia type 2B and sporadic disease) or the nondominant forearm brachioradialis muscle (in patients with multiple endocrine neoplasia type 2A). Adequate central node dissection is extremely difficult if the parathyroids are left in place with an adequate blood supply. There are nodes that are closely associated with the parathyroids and their blood supply. Attempts to leave the parathyroids in place result in either leaving central nodes in the neck, or leaving devascularized parathyroids. If the need for reoperation in the central compartment arises, the risk of subsequent hypoparathyroidism is negligible in a patient with a functioning autograft.

Alternatively, total thyroidectomy, parathyroidectomy, and central neck dissection may be performed as the initial procedure, with bilateral functional (levels II to V) neck dissection done as a second procedure in patients with persistent elevations of calcitonin and no evidence of distant metastatic disease.

As with any specialized procedure performed for an unusual clinical problem, these operations should be performed by surgeons who are familiar with the disease and who have expertise in the techniques described. For a surgeon unfamiliar with these techniques, we recommend diagnostic thyroid lobectomy, leaving the parathyroids undisturbed, with subsequent referral of the patient to an appropriate surgical specialist.

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Discussion

DR. GREGORY B. BULKLEY (Baltimore, Maryland): There are two sort of overriding concerns with medullary thyroid cancer that have to be taken into account before you start thinking about this disease. The first of these is that nodal metastases clearly seem to matter in this disease. Now I say that without really any absolutely documented proof that that is the case. But with the modern paradigm being, particularly with respect to breast cancer, that what you do when you take out nodes is all we are doing is staging the tumor, here is an example where we probably really make a difference. Let me remind the audience of something that we really already know. When we operate on colon cancer, even before the days of adjuvant therapy, we cured about half the patients with positive nodes. So fortunately for surgeons, taking out nodes really does matter therapeutically. It is just not a matter of staging.

The second important point with this disease, which Jeff Moley made clearly, is that there is effectively no adjuvant or no alternative form of radiation or chemotherapy for this disease. There have been sporadic reports, but they really don't work. So this is a disease that starts locally, stays regional, at least for some period of time, and is not amenable to any sort of systemic therapy in any significant degree that we are able to measure, and therefore, this is a disease for the surgeon.

Now the important contribution of this paper, to me, are two things, and I think Jeff made them very clear. One, that the intraoperative judgment of the surgeon is simply not reliable in this case. The sensitivity of an experienced surgeon—and gosh knows, these guys are experienced surgeons—is only 64%, and the specificity is only 70%. So, clearly, that is not an adequate standard, and we can no longer rely on our clinical judgment—"Gee, I will take some more nodes," or "I won't take those nodes." The second obvious important conclusion is that even nodes outside the traditional central lesion, whether ipsilateral or bilateral, are frequently positive.

Like many discussants, however, I have some questions and some caveats.

In the first place, your gold standard in this study was traditional surgical pathology looking at histologic sections. We know now that when we use more modern techniques for defining positive histology, whether we look for oncogenes or, in this case, we can stain for calcitonin, it is frequently possible to find microscopic evidence of disease in nodes far more frequently than even the most careful clearance and traditional pathologic resection. So aren't you really just underestimating the positivity of these nodes? And is this really a gold standard in 1998?

You have followed these patients for many years—many of the patients in this series, as you pointed out, Sam has been presenting them for years. You have given us no follow-up data on these patients, and you don't have a control series. I mean, your control, basically, was the surgeon's opinion *versus* the pathologist's opinion. Do you have any information about whether it really does—even though I got up here and said that I think it makes a difference to take out these nodes—do you have any evidence that it really does?

The reason that is so important is because we really need extremely long follow-up on these patients. Last year we presented a series here where we operated on patients with known metastatic disease, and those patients had symptom-free survival of 8.2 years, even with known disseminated metastatic disease that we knew before surgery couldn't be resected. So you are going to have to follow patients 10, 15, 25 years to know this, Jeff. You guys have been following these patients for 10, 15, 25 years since Sam has been there. You must have some data for this that you could share with us.

I appreciate this paper. I think it is particularly important and pertinent in terms of what it tells us about the distribution of nodes in our diagnostic accuracy. I think it is a very important contribu-

tion from that point of view. It doesn't help me as much as I wish, frankly, in terms of knowing the impact of our therapy on the long-term survival of these patients.

DR. RICHARD GOLDSTEIN (Nashville, Tennessee): I would like to commend Dr. Moley and his coauthor on another superb and thoughtful investigation, shedding new insights into medullary thyroid cancer, a disease for which the best hope for cure is to surgically remove all malignant cells. Hence, lymph node dissection does have an important role in the management of these patients.

I do have a few questions to pose to Dr. Moley and to press him a little in relation to how his results should be translated into the actual management of these patients.

If one is performing the initial procedure for medullary thyroid cancer and the palpable tumor measures greater than 1.0 cm, should these patients undergo bilateral neck dissections at that time?

My impression has been that in the past, if there was evidence of medullary thyroid cancer spreading outside of the neck, that the bilateral neck dissections were not performed. So, in other words, what role does evaluation of distant disease play? And therefore, should these patients undergo a total thyroidectomy, a central node dissection, and parathyroid autotransplantation at the time, at the initial time, followed by evaluation for disease outside of the neck? And then only if there is no evidence of disease outside the neck, should they undergo bilateral neck dissections?

Second, for patients with tumors, with palpable tumors of less than 1.0 cm, one out of four and four out of 12 of your patients had contralateral mets, or unilateral and bilateral tumors, respectively. If only one more patient in the unilateral group had contralateral metastases, had been positive, and the incidence in both groups would have been 33% or greater, could one not argue that this would suggest that all patients with palpable tumors, regardless of tumor size, should undergo central and bilateral neck dissections?

And, last, do you have any data that correlates MEN status *versus* sporadic disease and the spread of lymph node metastases in the neck? Some people believe that the MEN tumors are a little less aggressive, particularly MEN-2a. Do you have any data available on that?

DR. JEFFREY F. MOLEY (Closing Discussion): Answering Dr. Bulkley's question regarding using nontraditional techniques of evaluating lymph nodes—immunohistochemistry or possibly PCR amplification of gene products which are made by these tumors—we have not relied upon that because of the fact that the calcitonin assay is such an excellent indicator of the presence of residual disease postoperatively, first of all. And second of all, because we tend to remove a lot of lymph nodes, and our pathologists balk at the idea of having to cut thin sections and do immunohistochemistry on such large amounts of tissue, and argue that—I think correctly—that there is no proof that this information is really going to help in the management of the patient. So we have relied upon standard histologic examination and postoperative calcitonin levels.

In this series, of the 73 patients that were included in this analysis—and they were selected for patients who had bilateral dissections—the calcitonin levels were normal postoperatively in 33% exactly. And we are continuing to follow these patients closely.

Now these patients really started coming to Washington University with persistent or residual disease when Dr. Turcell first came in 1991, and I worked with him for 2 years and then took over that project in 1993. So we really don't have a 10- to 25-year follow-up on patients who have had extensive node dissections, because we have only been doing them since 1991.

I can tell you, though, that of my own personal series that was presented 2 years ago, 45 patients who I had done at that time—and now I have done 76 operations with curative intent—a third of the patients have postoperative calcitonin levels that are normal. And of those patients, several patients have gone on to develop a recurrence in the increase in the calcitonin level.

We have had two patients in that series of patients who were operated on die. It is going to take, as you said, 10 to 20 to 30 years of follow-up of these patients to really be able to determine the benefit. And I think if we can recruit a large enough number of patients, it might be reasonable to randomize patients into an observation *versus* a surgery arm, but we have not done that yet.

In answer to Dr. Goldstein's questions, for palpable tumors less than 1 cm, I would personally perform central and bilateral neck dissections. As I said, I think it would be reasonable for other surgeons to just do the central node dissection. And I think that the critical issue is to get the central node dissection done at the first operation. Because in a reoperative setting, the incidence of complications such as recurrent nerve injury, hypoparathyroidism, thoracic duct leak, is much higher than it is if the operation is done at the initial setting.

If the patient has a persistent elevation of calcitonin levels following that operation, then the lateral neck dissections can be done. And in our hands, these neck dissections have been done with extremely low morbidity and mortality. We don't do radical neck dissections. We do functional neck dissections, leaving the phrenic, the accessory nerve, the jugular vein, and the muscles intact. And the patients tolerate the procedures quite well.

As far as the correlation between MEN status *versus* sporadic disease, there was no difference in the incidence of metastases in patients of one group or the other. Of course, the patients with MEN had a higher incidence of bilateral disease in the thyroid at the time of presentation, so that group of patients is heavily weighted towards MEN-2a, 2b and familial medullary thyroid carcinomas.

I do believe that patients with distant metastases from medullary thyroid carcinoma who have MEN-2a and familial medullary thyroid carcinoma have a more benign course than patients with sporadic disease, but I don't have data to support that observation.